An Investigation of the Cognitive and Psychiatric Profile for People with Parkinson's Disease Without Dementia

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17 July 2008

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My heartiest congratulations on your achievement and best wishes for your future career.

Yours sincerely

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Abstract

Introduction: Idiopathic Parkinson's disease (PD) is a chronic and progressive neurodegenerative disorder that is characterised by motor symptoms. However, there is increasing awareness that a range of neuropsychiatric and cognitive problems also accompanys PD. The objective of this thesis was to examine the profile of neuropsychiatric and cognitive problems for patients with PD without dementia. Parkinson's disease patients who could be identified at the time of this study were invited to participate. Each patient was individually matched to a healthy control in terms of age, premorbid intelligence, and years of education. **Results:** Neuropsychiatric symptoms were common for this patient group, over 40% self-reported symptoms consistent with depression, 40% with physical fatigue, 38% with mental fatigue, 38% with apathy and 32% with sleep problems. More than 77% of patients with PD reported symptoms associated with at least one problem and over 46% with 3 or more problems. Increased symptoms consistent with depression and anxiety and the presence of hallucinations also predicted poorer quality of life after controlling for motor symptoms. However, the of level agreement between patient report and that of a person who know them well was low: 40.9% for apathy, 28% for hallucinations, 39% for depression, 25% for sleep problems and only 7.7% agreement for the presence of anxiety. To obtain an accurate profile of cognitive impairments patients were assessed on measures of higher order language ability and a broad range of commonly used cognitive tests. Overall, PD patients were impaired on aspects of higher-order language. However, results indicated that these deficits were not a primary effect of PD, but could be explained in terms of deficits in speed of information processing associated with the disease. Compared to healthy controls, PD patients also showed deficits on measures of executive function, working

memory, problem solving, and visuospatial skills. However, they were unimpaired on measures of planning, attention and memory/learning. Deficits in problem solving were only evident for tasks with a high visuospatial content and were no longer significant when visuospatial skills were controlled for. Further investigation indicated that planning in PD patients was not impaired in general and was dependent on the sensitivity of tests used. To further examine cognitive deficits, patients were divided into groups according to their cognitive performance. Three sub-groups of patients were identified that formed a continuum of cognitive impairment from none/mild to severe. Compared to controls, one subgroup showed no or minimal impairment (PD-NCI), a second group showed a more variable pattern of severe and mild impairments (PD-UCI), and a third group had evidence of severe impairment across most of the cognitive domains tested. This latter group was labelled PD-Mild Cognitive Impairment (PD-MCI). The PD-UCI and PD-MCI groups were also significantly different from their controls with respect to their ability to carry out functional activities of everyday living. The PD-MCI group had evidence of global cognitive decline, possibly reflecting a stage of pre-clinical dementia. The severity of cognitive deficits was not associated with other clinical and demographic characteristics such as motor impairments, age or disease duration. These results were confirmed when patients were retested one year later. **Conclusions:** Comorbid neuropsychiatric and cognitive problems are common for patients with PD prior to any overt signs of dementia. However, PD patients are heterogeneous with regard to their presentation and different subgroups of patients are identifiable based on cognitive performance. This information has both theoretical and clinical relevance.

Chapter 1 - Introduction

Abbreviations used in the text Chapter One

1) **AD** = Alzheimer's disease; 2) **GPi** = Globus pallidus interna; 3) **GPe** = external segment of the globus pallidus; 4) **MCI** = Mild Cognitive Impairment; 5) **PD** = Parkinson's disease; 6) **PDD** = Parkinson's disease with dementia; 7) **PD-MCI** = Parkinson's disease with Mild Cognitive Impairment; 8) **PD-UCI** = Parkinson's disease Uncertain Cognitive Impairment; 9) **PD-NCI** = Parkinson's disease No/Minimal Cognitive Impairment; 10) **PFC** = Pre frontal cortex; 11) **WM** = Working Memory; 12) **SAS** = Supervisory Attention System;13) **SN** = Substantia nigra ; 14) **SNc** = Substantia nigra pars compacta ; 15) **SNr** = Substantia nigra pars retculata; 16) **STN** = Subthalamic nucleus; 17) **WCST** = Wisconsin Card Sorting Test.

1.1 Overview

Idiopathic Parkinson's disease (PD) is a chronic and progressive neurodegenerative disorder that affects around 1/1000 individuals (Twelves, Perkins, & Counsell, 2003). The pathology of this disorder is focused on the substantia nigra and nigrostriatal tract, resulting in the motor symptoms that characterise this disorder (Braak & Braak, 2000). Onset occurs most commonly after the age of 50 and its incidence increases with advancing age (de Rijk et al., 1997). While PD is primarily characterised by motor dysfunction, signs of early cognitive disturbances are also a feature of the disease process (Brown & Marsden, 1990; Marsh, 2000; Shulman, Taback, Bean, & Weiner, 2001). The end consequence of this cognitive decline may be frank dementia. Indeed, research indicates that a substantial number of individuals with PD will progress to a diagnosis of dementia (see Emre, 2003 for review). However, there is also a substantial body of research that suggests that individuals with PD without overt signs of dementia, may be impaired on a number of cognitive tasks, with executive function deficits being prominent (see Brown & Marsden, 1990; Pillon, Boller, Levy, & Dubois, 2001 for reviews). Deficits in these facets of cognition, particularly in combination with other psychiatric symptoms, are especially important as it is likely that they will impact on other areas of cognitive ability, and affect the individual's functioning in everyday situations.

Although there has been abundant research regarding the cognitive and psychiatric outcomes, the precise nature of the decline in these areas of functioning in relation to PD, and hence their relationship to deficits in everyday living skills, are poorly defined. The proposed research was designed to generate novel information

on the cognitive and psychiatric profile of non-dementing PD patients, and the relationship between these deficits and everyday living skills.

A particular focus of the research was to identify a discrete battery of cognitive and psychiatric measures that would be able to detect people with PD who were experiencing clinically significant problems who could be at risk of later dementia. The ability to identify this particular group of people with PD will provide an opportunity for intervention. Intervention strategies could be aimed at reducing the impact of cognitive and psychiatric deficits which are a significant cause of caregiver distress and frequently lead to premature placement in care units (Aarsland, Larsen, Karlsen, Lim, & Tandberg, 1999; Aarsland, Larsen, Tandberg, & Laake, 2000). In addition, more recent research has indicated that cognitive decline may be delayed by the use of drug and behavioural interventions (Aarsland, Larsen, Karlsen, Lim, & Tandberg, 1999; Aarsland, Larsen, Tandberg, & Laake, 2000). Therefore, early detection of cognitive and psychiatric deficits that may signal the early decline to dementia could have personal, social and economic value.

As mentioned previously, the research regarding the non-motor deficits in PD is voluminous. However, to provide sufficient background for the current research, this literature review will first provide general background information including epidemiology and characteristic motor symptoms. The focus of the review will be an examination of the major theories used to account for the deficits associated with this disorder, and an overview of the cognitive and psychiatric outcomes that have been reported. The difficulties connected with research in this area will also be covered as they have important implications in terms of explaining the inconsistencies inherent in the current literature. Further, this information will be used to inform appropriate

methodologies for this project which will endeavour to overcome many of the shortcomings of previous research. Each of these perspectives is important as their synthesis is required to adequately inform the current research hypothesis.

1.2 Epidemiology

Epidemiology has been intensively investigated in an effort to identify patterns that may provide information regarding the cause of PD and lead to appropriate interventions (Di Monte, Lavasani, & Manning-Bog, 2002). A number of causes have been suggested, e.g. environmental and genetic influences (see Di Monte, Lavasani & Manning-Bog, 2002 for review). However, the slow and insidious onset that is characteristic of this disorder makes the identification of any causal links extremely difficult. Further, differences in study design and diagnostic criteria make any comparisons across studies problematic (Marion, 2001; Twelves, Perkins, & Counsell, 2003). Thus, despite considerable research interest, the etiology of PD remains unknown. Nonetheless, PD is a relatively common disease with significant health costs associated with its management, and it is therefore important to have accurate information regarding its incidence and prevalence rates.

Incidence and prevalence rates have been investigated in a number of countries. While many studies rely on a review of medical records, door to door surveys suggest that over 20% of cases remain undetected in the community (de Rijk et al., 1997). It is therefore not surprising that estimates of incidence and prevalence vary widely depending on the case ascertainment method used (de Rijk et al., 1997; Guttman, Slaughter, Theriault, DeBoer, & Naylor, 2003; Twelves, Perkins, & Counsell, 2003). In a recent review, von Campenhausen et al., (2005) stated that higher quality studies, (i.e., those that used an established diagnostic criteria, included

the entire age range of the population, and used screening by an experienced neurologist) reported prevalence rates of 108 to 257/100,000 and incident rates of 11-19/100,000. However, even when the most rigorous design is used, a significant number of cases may be misdiagnosed (Schrag, Ben-Shlomo, & Quinn, 2002).

Despite variations in the reported incidence and prevalence of this disorder, it has been consistently reported that rates steadily increase with age and that disease symptoms usually appear after 50 years of age (Bower, Maraganore, McDonnell, & Rocca, 2000; de Rijk et al., 1997; MacDonald, Cockerell, Sander, & Shorvon, 2000; Mayeux et al., 1995). Further, while PD is thought to affect all races equally (with any discrepancy between races generally thought to be associated with case ascertainment methods), there is a preponderance of males to females, with males having a 1.5-2 times increased likelihood of being diagnosed with PD (Guttman, Slaughter, Theriault, DeBoer, & Naylor, 2003; Mayeux et al., 1995; Wooten, Currie, Bovbjerg, Lee, & Patrie, 2004).

1.3 Motor Symptoms

Tremor, rigidity, bradykinesia and postural instability are considered to be the cardinal features of PD (see 1.3.1 for description of motor symptoms). However, presenting motor symptoms vary considerably for each individual and may have particular importance for the identification of PD subtypes (See Table 1 for common motor features associated with PD). Initial diagnosis is based on the evaluation of presenting physical symptoms and their history but a definitive diagnosis of PD can only be made on the basis of autopsy evidence which includes the degeneration and loss of pigmented cells in substantia nigra pars compacta (SNc) and the presence of Lewy bodies (Kang et al., 2005). Clinical symptoms of PD only manifest when

nigrostriatal dopamine depletion is at around 80%, and approximately 60% of the dopaminergic neurons in SNc have been lost (Gibb, 1997).

Table 1: Common motor symptoms associated with Parkinson's disease (Jankovic, 2003).

Tremor	Sialorrhea (excessive salivation)
Rigidity	Respiratory difficulties
Bradykinesia	Festination
Postural instability	Freezing
Masked facies	Micrographia
Hypophonia	Decreased blink rate
Dysphagia	Levodopa induced dyskinesias

A number of neurodegenerative diseases can be mistaken for PD. These are generally referred to as Parkinson plus syndromes and include: progressive supranuclear palsy, cortical-basal degeneration, multiple system atrophy, dementia with Lewy body and vascular Parkinsonism. However, research indicates that the degree of clinical diagnostic accuracy is higher when more stringent criteria are applied such as the United Kingdom Parkinson's Disease Society Brain Bank Diagnostic Criteria for Parkinson's disease (see Table 2) (Jankovic, 2003).

Table 2: United Kingdom Parkinson's Disease Society Brain Bank Clinical Diagnostic Criteria (Reproduced from Hughes, Daniel, Kilford, & Lees, 1992).

Inclusion Criteria

- Bradykinesia
- Plus at least one of the following
  - Muscular rigidity
  - 4-6 Hz rest tremor
  - Postural instability not caused by primary visual, vestibular, cerebellar or proprioceptive dysfunction

Exclusion Criteria

- History of repeated head injury
- History of repeated stroke
- History of definite encephalitis
- Oculogyric crises
- Neuroleptic treatment at onset of symptoms
- More than one affected relative
- Sustained remission
- Strictly unilateral features after 3 years
- Supranuclear gaze palsy
- Cerebellar signs
- Early severe autonomic involvement
- Early severe dementia
- Babinski sign
- Cerebral tumour or communicating hyrocephalus on CT scan
- Negative response to large doses of levodopa
- MPTP exposure

Supportive Criteria

Three or more of the following for diagnosis of definite PD:

- Unilateral onset
- Resting tremor
- Progressive disorder
- Responsive to levodopa
- Severe levodopa-induced chorea
- Levodopa reponse for ≥ 5 years
- Clinical course ≥ 10 years

1.3.1 Description of Characteristic Motor Symptoms

Tremor and bradykinesia are the two most common initial symptoms (Uitti, Baba, Wszolek, & Putzke, 2005). Tremors occur predominantly at rest, with a frequency of 4-6Hz, and diminish on action (Jankovic, 2003). However, not all patients with PD manifest a resting tremor as the presenting symptom, and 15% will never manifest a tremor during the entire course of the disease (Jankovic, 2003; Kang et al., 2005). The etiology of the resting tremor remains unknown (Carr, 2002). Patients with PD may also develop a postural tremor, 5-8Hz, that occurs during activity (Jankovic, 2003).

Bradykinesia is defined as a slowness of movement. It is often used interchangeably with hypokinesia, which refers to slowed movements, but with the addition that the movements performed are smaller than intended (e.g. micrographia), and with akinesia, referring to a lack of spontaneous movement (e.g. lack of spontaneous arm swing when walking) (Berardelli, Rothwell, Thompson, & Hallett, 2001). Bradykinesia is thought to result from deficient output from the Basal Ganglia to the cortex (Berardelli, Rothwell, Thompson, & Hallett, 2001).

Rigidity, also a prominent feature of PD, refers to the increased tone or stiffness in the muscles that are resistant to passive movement, and may result in a subjective feeling of tightness and pain in the muscles. The fourth cardinal feature is postural instability, a tendency to lose balance with propulsion and retropulsion. Postural instability is more common in the later stages of the disease and is generally accompanied by festination (i.e. short shuffling steps).

The cause of postural instability is not known, but has been attributed to the degeneration of the globus pallidum, reduced or absent vestibular responses, or abnormal postural reflexes (Jankovic, 2003).

As stated at the beginning of this section, individuals vary greatly in their presentation of motor symptoms and it has been suggested that differences in motor presentation may be indicative of differences in disease progression (Kang et al., 2005). Indeed, two recent studies have suggested that different subgroups of patients with PD can be identified by a combination of motor and cognitive symptoms (Graham & Sagar, 1999; Lewis et al., 2005).

1.4 Theory of Deficits Associated with Parkinson's disease

1.4.1 The Structure of the Basal Ganglia

Dysfunction of the basal ganglia system is considered key to the motor, cognitive, and psychiatric deficits associated with Parkinson's disease. Therefore, a brief description of the basal ganglia, its structure and changes that occur with PD is important in terms of understanding the possible deficits that are associated with this disorder.

The basal ganglia are a group of interconnected subcortical structures in the forebrain. Although the structures that are considered to be part of the basal ganglia vary, there is general agreement that they include the caudate nucleus, putamen (these two structures are often referred to as the striatum), globus pallidus (globus pallidus and putamen are sometimes referred to as the lenticular nucleus) and the nucleus accumbens (Ring & Serra-Mestres, 2002). Many authorities also include the substantia nigra, subthalamic nucleus and the amygdala as structures of the basal

ganglia (Haber, 2003; Herrero, Barcia, & Navarro, 2002; Ring & Serra-Mestres, 2002; Yelnik, 2002). The ventral striatum, comprising the ventromedial caudate, ventral putamen, nucleus accumbens and olfactory tubercle, is a term more recently used to describe parts of basal ganglia that are closer to limbic structures (Haber, 2003). Traditionally, the basal ganglia have been considered to be involved primarily in movement, but it is now recognised that they also play a vital role in cognitive, behavioural, and psychiatric functions (Ring & Serra-Mestres, 2002).

1.4.2 Deficits Associated with Basal Ganglia Dysfunction

Dysfunctions within the basal ganglia are implicated in a range of movement, psychiatric, and cognitive problems, often resembling deficits usually associated with lesions of the prefrontal cortex (Aarsland et al., 1999; Adler, 2005; Bhatia & Marsden, 1994; Burn, 2002b; Cummings, 1992; Eslinger & Grattan, 1993; Friedman & Chou, 2004; Pillon, Boller, Levy, & Dubois, 2001). Recent reviews suggest different regions of the basal ganglia are associated with diverse range of functions. For example, the ventral regions of the basal ganglia are key in reward and reinforcement, the central regions with cognitive functions that include procedural learning, and working memory, while dorsolateral portions of the striatum control movement (Haber, 2003).

This general topography has been supported to some extent by clinical cases. Bhatia and Marsden (1994) reviewed available literature and reported outcomes for 240 patients who had experienced focal lesions to different basal ganglia structures. Of the 240 patients, 111 had behavioural problems, including abulia (defined by the authors as apathy with loss of initiative and spontaneous thought and emotional responses), disinhibition, obsessive compulsive disorder, speech disorder and

depression. Abulia was the most common behaviour disturbance, and 13% of the 240 patients had symptoms consistent with this disorder. The most frequent motor disorders included dyskinesia, Parkinsonism, changes in muscle tone (muscular rigidity) and resting tremor. Deficits varied depending on the position of the lesions experienced by the patients.

From clinical cases such as those described, it is possible to make some general assumptions about lesions in the basal ganglia. For example, the authors reported that lesions confined to the caudate rarely caused motor problems and were more likely to cause problems with behaviour, whereas lesions in the lenticular nuclei rarely caused behavioural problems, but were highly likely to cause motor problems.

1.4.3 Contemporary Model of the Basal Ganglia

Because early theorists emphasised the role of the basal ganglia in motor functioning, its function was originally conceptualised as receiving information from diverse areas of the sensory and association cortices, and funnelling this information to the motor cortex. However, this view has been substantially revised over the past 20 years. One of the most influential models has been that suggested by Alexander and colleagues (1986; 1990). These authors propose that the basal ganglia are involved in at least 5 parallel loops with the cerebral cortex. Two of these loops are associated with the control of movement, and involve areas of the cerebral cortex associated with motor and oculomotor functioning. The remaining three loops are involved in cognition and behaviour, and include dorsolateral prefrontal, lateral orbitofrontal and the anterior cingulate regions of the cerebral cortex (Alexander & Crutcher, 1990; Alexander, DeLong, & Strick, 1986). Each basal ganglia-thalamocortical loop receives input from multiple functionally-related cortical areas

and have been described as being closed, in that each receives input from and projects output to a specific cortical area (Alexander, DeLong, & Strick, 1986; Middleton & Strick, 2000a). However, while each of the loops was conceptualised as segregated, they also receive inputs from, and output to, other structures (Alexander, DeLong, & Strick, 1986; Haber, 2003; Middleton & Strick, 2000a). Since its original inception, the model has been developed to include both direct and indirect pathways (Albin, Young, & Penney, 1989).

The motor circuit is most commonly used to facilitate an understanding of how the basal ganglia function (see Figure 1). The direct pathway, which comprises mainly D1-type receptors, projects to the main output nuclei of the basal ganglia, the globus pallidus interna (GPi) and the substantia nigra pars reticulata (SNr). The GPi/SNr inhibits targets in thalamus and brain stem, with an excitatory effect on thalamo-cortical projection (Yelnik, 2002). The indirect pathway, which comprises mainly D2- type receptors, projects primarily to the external segment of the globus pallidus (GPe), which outputs to the subthalamic nucleus (STN). Output from the STN to the GPi/SNr is excitatory, with an inhibitory effect on the thalamo-cortical projection (Lewis, Caldwell, & Barker, 2003; Yelnik, 2002). When functioning effectively, the two pathways work in unison to create a balanced system. More recently, a number of deviations to the classic basal ganglia model have been suggested, including projections to the pendunculo-pontine nucleus and the spinal cord (Delwaide, Pepin, De Pasqua, & de Noordhout, 2000).

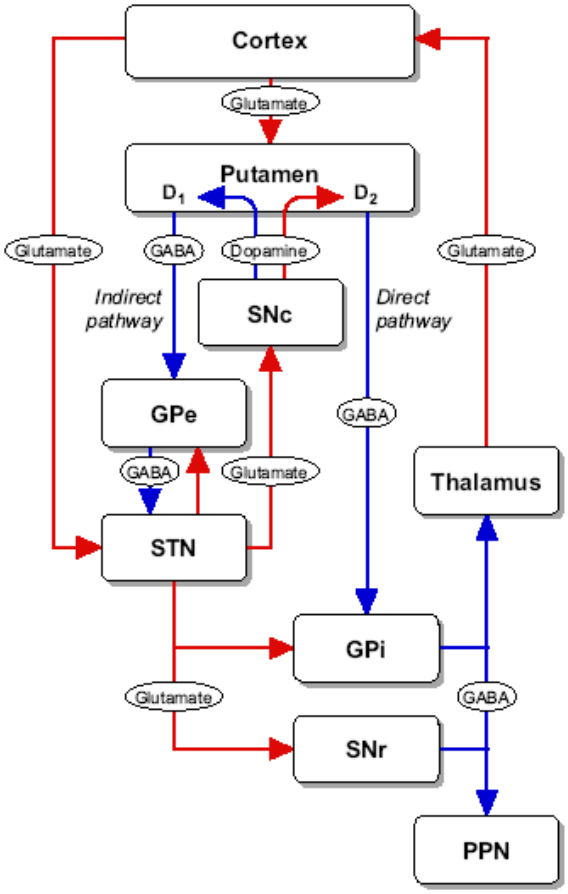


Figure 1: A schematic representation of the basal ganglia using the motor circuit. The direct pathway, represented by the blue lines, projects to the globus pallidus interna (GPi) and the substantia nigra pars reticulata (SNr). The GPi/SNr inhibits targets in thalamus and brain stem with an excitatory effect on thalamo-cortical projection. The indirect pathway represented by the red lines, projects primarily to the external segment of the globus pallidus (GPe) which outputs to the subthalamic nucleus (STN). Output from the STN to the GPi/SNr is excitatory, with an inhibitory effect on the thalamo-cortical projection (Adapted from Lewis, Caldwell, & Barker, 2003; and Obeso et al., 2000).

1.4.5 Limitations of the Model

While this model has provided a useful framework from which to conceptualise the basal ganglia and associated disorders, it is important to be aware of some of the model's limitations (see Hauber, 1998 and Saint-Cyr, 2003 for comprehensive reviews). For example, it is clear that a degree of information integration occurs within the basal ganglia, given that the multiple related cortical areas project to a given sub-region of the striatum, and input structures (striatum) comprise of approximately 30 times more neurons than the output structures (SNr, and the GPi, Hauber, (1998)). However, the current model lacks explanatory value in terms of how this information is integrated (Saint-Cyr, 2003).

Further, a number of more recent findings are not easily explained by the model. For example, D1 and D2 neurons have been found to "co-localize" on striatal neurons and all striatal neurons that project to the GPi also project to the GPe. Therefore, the conceptualisation of the D1 /D2 neurons in the basal ganglia as being either excitatory or inhibitory is considered to be an over-simplification (Bar-Gad & Bergman, 2001).

Other aspects of the original model remain a matter of debate, including the extent to which the loops are segregated, whether there is functional overlap, and whether there are additional basal ganglia-thalamocortical loops (Chesselet & Delfs, 1996; Levy et al., 1997; Saint-Cyr, 2003; Wichmann & DeLong, 2003). Major regions of the cortex project to overlapping areas of the striatum, suggesting that the circuits are not totally segregated on the basis of cortical input (Saint-Cyr, 2003). Also, there are projections back to the cortex from the GPe and projections from the basal ganglia to the brain stem. However, the role of these open circuits is not

adequately explained by the model (Bergman & Deuschl, 2002; Delwaide, Pepin, De Pasqua, & de Noordhout, 2000). Despite the limitations covered above, anatomical observations and clinical studies have provided wide support for the model suggested by Alexander and colleagues, and it has been used to inform both research and surgical interventions (Middleton & Strick, 2000a, , 2000b).

1.5 Parkinson's disease and the basal ganglia

1.5.1 The Dopamine Theory

Parkinson's disease is characterised by the depletion of dopamine due to the degeneration of dopaminergic neurons in the SN (see Figure 2), and not surprisingly, the dopamine theory is used to account for the deficits reported with this disorder. It is therefore essential to understand how this theory has been used to explain both the motor and non-motor aspects of this disorder.

Motor deficits are characteristic of PD and the dopamine theory explains this in the following way. It is suggested that the direct and indirect pathways, described earlier, operate on the GPi/SNr. The nigrostriatal denervation leads to over-activity of GPi/SNr (Lewis, Caldwell, & Barker, 2003; Yelnik, 2002), with an overall inhibitory effect on the thalamus. This in turn leads to an under-activation of the motor cortex and a reduction or absence of movement as seen by the presence of bradykinesia or akinesia associated with PD (Lewis, Caldwell, & Barker, 2003; Obeso et al., 2000).

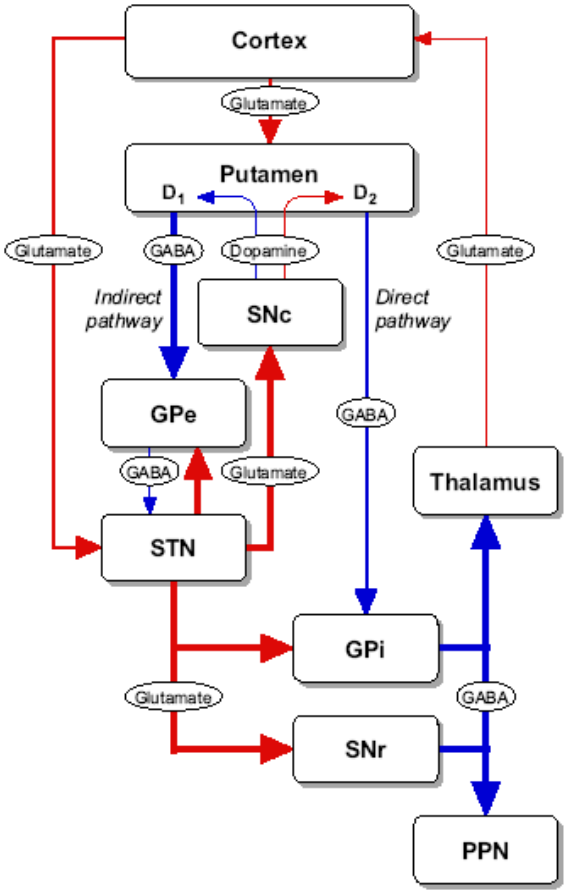


Figure 2: A schematic representation of the basal ganglia using the motor circuit, for a patient with Parkinson's disease.

A depletion of nigorstriatal dopaminergic neurons in the substantia nigra pars compacta (SNc) is represented by the thin lines. The direct and indirect pathways operate on the GPi/SNr. The nigrostriatal denervation leads to over-activity of GPi/SNr with an overall inhibitory effect on the thalamus leading to an under-activation of the motor cortex (Adapted from Lewis, Caldwell, & Barker, 2003; and Obeso et al., 2000).

The cell bodies of the nigrostriatal dopaminergic neurons are located in the SNc and project primarily to the putamen, but also to the caudate. Research suggests that Parkinson's disease first affects the posterior putamen, then the anterior putamen and the caudate nucleus (Bruck, Aalto, Nurmi, Bergman, & Rinne, 2005; Jellinger, 1999). This explains why motor symptoms are often the first signs for people with PD (Middleton & Strick, 2000b). In contrast, dopamine depletion associated with Huntington's disease begins in the anterior caudate and initial problems are usually cognitive in nature (Lawrence et al., 1998; Lawrence et al., 1996).

Interestingly, it has been reported that neuronal loss in the SN in people with PD is not evenly distributed. Neurons in the ventrolateral part of the SN degenerate to a greater extent than those in the medial part. This has important implications in terms of the projections from the SN. Research indicates that different types of PD, (e.g., akinetic-rigid type and tremor-dominate type) show different patterns of neuronal loss in the SN, and it is has been suggested that these different patterns of neuronal loss could explain the heterogeneity of motor symptoms (Damier, Hirsch, Agid, & Graybiel, 1999; Rinne, 1993).

Consistent with the dopamine theory, most medications used to control the motor symptoms that characterise PD are based on dopamine replacement therapy. These treatments, at least in the early stages of the disease, ameliorate many of the motor symptoms, with symptoms only re-appearing at the "end of dose". Further, surgical procedures based on the dopamine model have been reported to be highly successful for some patients. Neurotoxic models have also supported the role of dopamine in the motor symptoms associated with PD (Dauer & Przedborski, 2003).

1.5.2 Dopamine Theory, Cognition and Behaviour

Dopamine depletion has also been associated with deficits in cognition and behaviour seen in PD. It is therefore essential to be aware of the current theories used to explain this link. As mentioned previously, the dorsolateral, orbitofrontal and anterior cingulate circuits, outlined by Alexander, DeLong, and Strick (1986), have been associated with behavioural and cognitive disorders (see Table 3). Each of these circuits share the same features as the motor circuit described earlier, with direct and indirect pathways, each loop being segregated, and arising from and projecting to the same area of the cortex (see Figure 3 for a diagrammatic representation of the closed circuit for each pathway. Only the direct circuit is shown). A large body of research supports the role of these circuits in cognitive and behavioural functioning (see Owen, 2004a for review). Also, lesions to the cortical areas and at other points of the circuits have been reported as having similar effects. Indeed, people with PD exhibit many of the deficits associated with dysfunction of the basal thalamo-cortical loops outlined here (deficits are covered in detail in section 1.4). Given the clear association between motor dysfunction in PD and dopamine depletion, it would be expected that an equally clear relationship would be evident for cognitive and behavioural deficits, however, this is not the case (see Table 4). Indeed this inconsistent association has led researchers to suggest that dopamine plays an indirect or moderating role in the cognitive and behavioural deficits associated with PD (Mattay et al., 2002).

Table 3: Cognitive and behavioural problems associated with dysfunction in the three frontal-sub-cortical circuits (Chow & Cummings, 1999).

Circuit	Dysfunction	Impairments
Dorsolateral Prefrontal circuit	*Executive functions*	• Poor organisational strategies • Poor memory search strategies • Stimulus bound behaviour/Environmental dependency • Impaired set shifting and maintenance • Poor working memory
Anterior Cingulate circuit	*Socially appropriate behaviour*	• Personality change • Emotional incontinence • Impulsivity • Irritability • Mood disorders
LateralOrbitofrontal circuit	*Motivated behaviour*	• Apathy • Poverty of spontaneous speech • Poor response inhibition • Reduced creative thought • Akinetic mutism

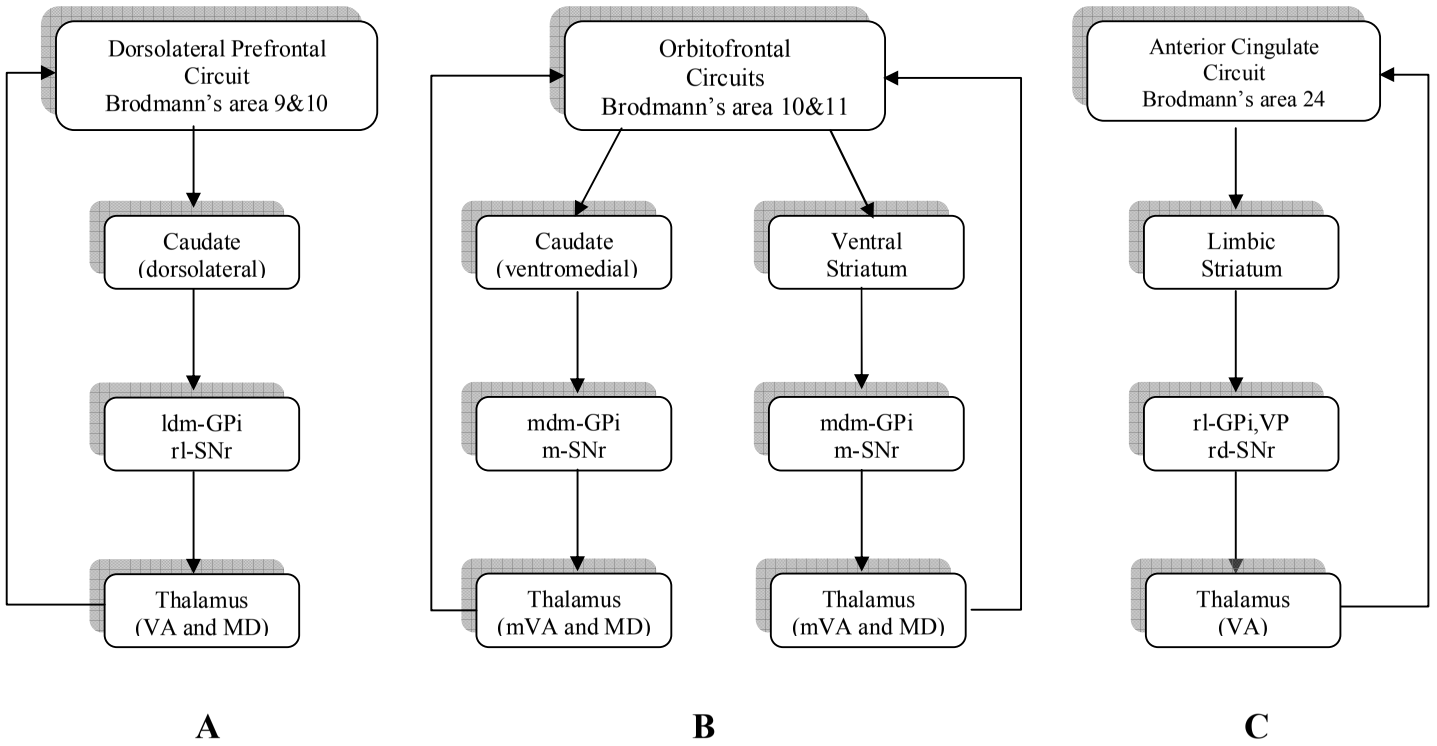


Figure 3: Direct pathways of the frontal-subcortical circuits (Adapted from Tekin & Cummings, 2002).

Frontal areas are identified using Brodmann's Area classification. Abbreviations are based on Alexander et al (1986), GPi-internal segment of the globus pallidus; MD- mediodorsal; mdm medial dorsomedial; m-medial; rd-rostrodorsal; rl-rostrolateral;SNr-Substantia nigra pars reticulate; VA-Ventral anterior, VP-Ventral pallidum.

1.5.3 Effects of Medications on Cognitive and Behavioural Symptoms

In contrast to the ameliorating effects of dopamine replacement on motor symptoms, a more complex pattern is seen for cognitive and behavioural deficits. Indeed, L-dopa medications (L-Dopa is a precursor to dopamine which, unlike dopamine itself, easily crosses the blood brain barrier) have been reported as helping, hindering or having no effect on non-motor symptoms (see Table 4) (Cools, 2006; Kulisevsky et al., 1996; Pillon, Czernecki, & Dubois, 2003).

Table 4: Effect of L-dopa on cognition and behaviour (Adapted from Pillon, Czernecki, & Dubois, 2003).

Status	**Reference**
Improvement "on" state	
Apathy	(Czernecki et al., 2002)
Cognitive Flexibility	(Cools, Barker, Sahakian, & Robbins, 2001a, , 2003)
Memory	(Cooper et al., 1992)
Tower of London	(Cooper et al., 1992)
Working memory	(Cooper et al., 1992; Costa et al., 2003; Fern-Pollak, Whone, Brooks, & Mehta, 2004; Mattay et al., 2002)
Deterioration "on" state	
Decision making	(Cools, Barker, Sahakian, & Robbins, 2003)
Memory	(Poewe, Berger, Benke, & Schelosky, 1991)
Errors on choice reaction time	(Schubert et al., 2002)
Probabilistic reversal learning	(Cools, Barker, Sahakian, & Robbins, 2001a)
Wisconsin Card Sorting Test	(Kulisevsky et al., 1996)
No change "on" state	
Cognitive slowing	(Press, Mechanic, Tarsy, & Manoach, 2002)
Memory	(Kulisevsky et al., 1996; Lange et al., 1992)
Reward association learning	(Czernecki et al., 2002)
Visual Learning Discrimination Task	(Lewis, Slabosz, Robbins, Barker, & Owen, 2005)

It is clear then that the dopamine theory alone is insufficient to explain the non-motor deficits associated with PD. Therefore, a brief overview of the theories used to explain the cognitive and psychiatric deficits associated with this disorder is provided.

1.5.4 "Overdose" Hypothesis

While a number of explanations have been offered regarding the inconsistent effects of dopamine on cognitive and behavioural symptoms associated with PD, one of the most compelling is the "overdose" hypothesis. It has been suggested that the variable outcomes in terms of cognitive and behavioural deficits is related to the pattern of depletion of dopaminergic neurons within the substantia nigra (SN). As stated earlier, the neuronal loss in the SN is not evenly distributed (Damier, Hirsch, Agid, & Graybiel, 1999; Haber, 2003; Rinne, 1993). Each of the circuits shown in Figure 3 receive projections from different regions of the SN. This observation has given rise to the "overdose" hypothesis. This hypothesis suggests that levels of dopamine required to remedy deficits will change throughout the course of the disease (Cools, 2006; Kulisevsky, 2000). For example, motor symptoms appear first, but levels of dopamine required to remedy the depletion of dopamine in the motor circuits may result in an "overdosing" of the cognitive circuits, with a resultant deleterious effect on cognitive performance. As stated earlier, projections to the putamen (associated with the motor circuits) have been found to deteriorate prior to the projections to the caudate (associated with cognitive functioning). Further, within the caudate there is a progression of loss of dopamine projections that are more severe in the ventrolateral part of the caudate nucleus that projects to the dorsolateral pre-

frontal cortex. Less affected are the cells in the ventral striatum that project to the anterior cingulate (Cools, 2006).

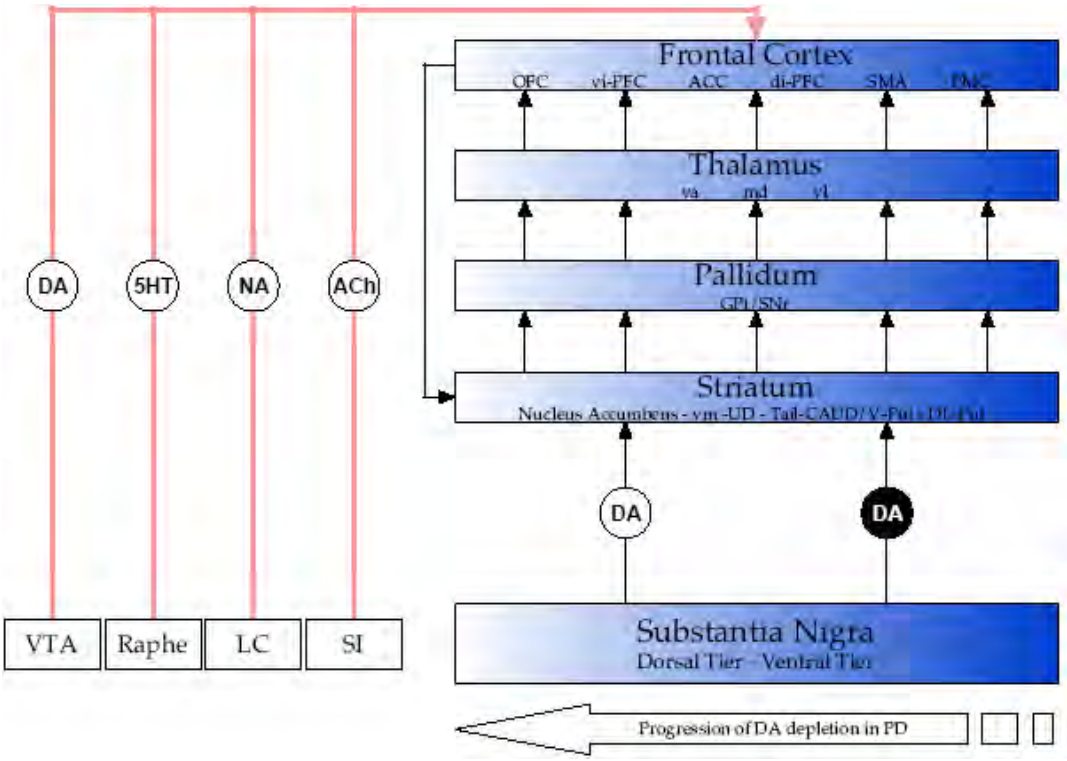


Figure 4: Schematic of the neurochemical pathology in Parkinson's disease.

Parkinson's disease is characterised by motor deficits and depletion of dopamine beginning in the pre and supplementary motor areas. The blue shading represents the progression of dopamine depletion in the basal ganglia-thalamocortical loops (reproduced from Cools, 2006). (Abbreviations: Ach=acetylcholine; ACC=anterior cingulate nucleus; DA=dopamine; dl-PFC= dorsolateral prefrontal cortex; DL-Put=dorsolateral putamen; Gpi=internal segment of the globus pallidus; LC=locus coeruleus; NA=noradrenaline; OFC=orbitofrontal cortex; PFC=prefrontal cortex;PMC= premotor cortex; SMA= supplementary motor area; SI=substantia innominata; Snr= substantia nigra pars reticulate;Tail-CAUD=tail of the caudate nucleus; V-Put=ventral putamen; va=ventral anterior nucleus; md=dorsomedial nucleus; vl=ventrolateral nucleus; vl-PFC=ventrolateral prefrontal cortex; vm-CAUD=ventromedial caudate nucleus; VTA=ventral tegmental area.

In addition to a progressive loss of dopamine in the associated frontal circuits, as shown in the above schematic, it has been proposed that other neurotransmitters are also depleted with progressive stages of the disease (Cools, 2006). However, other authors have suggested that the depletion of neurotransmitters other than dopamine (e.g. serotonin) may occur early in the disease process, and this may explain why symptoms associated with neurotransmitters other than dopamine (e.g., depression) may, in some cases, predate the onset of motor symptoms (Leentjens, 2004; Shiba et al., 2000).

1.5.5 Abnormalities of Other Structures and Systems

In addition to the main closed circuits, the frontal lobes are reciprocally connected to functionally similar areas of the brain via a number of open afferent and efferent connections (see Table 5. For a full account of the major and minor afferent and efferent connections of the frontal-subcortical circuits see Chow & Cummings, 1999). While the degeneration of the dopaminergic neurons are considered to be a hallmark feature of PD, the characterisation of this disorder as being isolated to the dopamine system is considered to be misleading (Braak & Braak, 2000). Evidence of abnormalities in other subcortical structures (including the loss of noradrenergic neurons in locus coeruleus, serotonergic neurons in the dorsal raphé nucleus, and cholinergic neurons in the nucleus basalis of Meynert), are evident from the early stages of the disease process (Braak & Braak, 2000; Jellinger, 1999; Murai et al., 2001; Slaughter, Slaughter, Nichols, Holmes, & Martens, 2001). Furthermore, there is strong evidence that the mesocortical dopaminergic system also contributes to deficits in cognitive and behavioural functioning (Mattay et al., 2002). The mesocortical dopaminergic system arises from the ventral tegmental area with direct

projections to the frontal cortex. Depletion of these projections has also been found in people with PD (Marsden, 2006). This diverse pattern of degeneration is thought to underlie heterogeneous, cognitive and psychiatric features of PD (Jellinger, 1999; Marsh, 2000).

Table 5: Major open afferent and efferent connections of the frontal-subcortical circuits, using Brodmann's area classification (Chow & Cummings, 1999).

	Dorsolateral Circuit	**Orbitofrontal Circuit**	**Anterior cingulate Circuit**
Major open afferent connections	Dorsofrontal area 46	Superior temporal area 22	Hippocampus
	Parietal area 7a	Orbitofrontal area 12	Entorhinal area 28 Perirhinal area 35
Major open efferent connections	Dorsofrontal area 46	Orbitofrontal area 12	Substantial nigra (pars compacta)
	Anterior frontal area 8	Mediofrontal area 25	Medical subthalamic nucleus
		Mediofrontal area 32	Lateral Hypothalamus

1.6 Cognitive Deficits associated with Parkinson's disease

1.6.1 Overview

A major focus of this thesis is the development of a cognitive and neuropsychiatric profile of PD patients. It is therefore pertinent at this point to review the major literature regarding deficits in these areas of functioning. There are a number of difficulties associated with research in this area, and it is important to review the literature in light of these.

1.6.2 Difficulties with the research in this area

Over the past 20 years there has been considerable interest in identifying the cognitive and behavioural consequences of PD (Taylor & Saint-Cyr, 1995). However, there is a great deal of inconsistency in the literature regarding the precise nature and extent of these deficits (Taylor & Saint-Cyr, 1995). Brown and Marsden (1990) suggest that the inconsistency in the literature most likely reflects the heterogeneity of tasks employed in testing PD patients, and the varying levels of complexity and processing demands of the different tasks. Moreover, tasks that are traditionally used to assess cognitive functions (executive functions, language and memory) rely on multiple aspects of mentation, but many studies have relied on single tests to either prove or disprove a deficit in a particular area of functioning. Furthermore, there is a lack of consistency regarding the way in which different cognitive skills have been operationalised (Taylor & Saint-Cyr, 1995).

Another potential cause of inconsistency in findings is that studies vary in terms of inclusion criteria, and groups are often heterogeneous in presentation. Also, the effects that different medications used to treat PD may have on cognition are often not considered (Taylor & Saint-Cyr, 1995). Moreover, much of what is known about the range of neuropsychological deficits associated with PD relies on a compilation of outcomes for different groups of patients. These groups differ with respect to a number of characteristics including level of motor impairment, age, and stage of disease. A much more consistent understanding of cognitive problems may emerge if a single group was used to examine all potential domains of impairment.

Despite the limitations in the literature, a general pattern of cognitive domains that are more likely to be impaired in patients with PD has been identified. These

include visuoperception/visuospatial ability, speed of mental processing, memory, learning, and executive functions (including, planning, working memory, verbal fluency and attention). Impairments in some areas of functioning are evident even from the early stages of the disease (Levin & Katzen, 1995). It has been suggested, given the consistency with which deficits in executive functions have been reported for patients with PD, that problems with areas such as memory and language may be secondary to these (Bondi, Kaszniak, Bayles, & Vance, 1993b). However, the nature of any core cognitive deficit in PD patients remains a matter of debate, with some researchers suggesting that deficits in attentional control represent the primary deficit while others propose working memory or inhibition.

The literature in the area of cognitive outcomes in PD is extensive, and there are several recent comprehensive reviews (Levin & Katzen, 1995; Owen, 2004a; Pillon, Boller, Levy, & Dubois, 2001; Zgaljardic, Borod, Foldi, & Mattis, 2003). Therefore, this review will focus on providing an overview of the current understanding of cognitive deficits associated with PD without dementia, with reference to the major articles in the area. A major purpose of this part of the review was to inform the test selection for the current project.

1.7 Executive Functions

1.7.1 Overview

A number of executive-type skills have been assessed in patients with PD. However, deficits in planning, working memory, and attention have been suggested as core deficits in patients with PD, and there has been considerable research interest in these skills (these are reviewed in more detail here).

The prefrontal cortex, and more specifically the dorsolateral prefrontal cortex, is considered to have a pre-eminent role in the performance of executive functions (Fuster, 2000). The prefrontal cortex is unique in that it is the only cortical area to receive information from all sensory, cortical, and motor systems, as well as sub-cortical structures including the limbic system and basal ganglia (Fuster, 2000). The effective processing of this information enables an individual to integrate cognitive and perceptual processes across time and space and update goals in the face of new information, in other words, an executive function (Roberts & Pennington, 1996). While there is no single agreed definition for executive functions (Salthouse, 2005), a wide range of skills and abilities including planning, working memory, decision making, and goal directed behaviour, flexibility, attention, self-monitoring, and control of ongoing behaviour are considered to be subsumed under this umbrella term (Samango-Sprouse, 1999).

1.7.2 Working Memory

Given the substantial number of connections between the prefrontal cortex and the basal ganglia, and the essential contribution of the prefrontal cortex to working memory (Bor, Duncan, Lee, Parr, & Owen, 2005), it is not surprising that there has been extensive research on the link between deficits in working memory (WM) and PD. Working memory refers to the ability to temporarily store and manipulate multiple aspects of information required for higher order cognitive tasks (Baddeley, 1992). The term WM is generally considered to encompass and expand the concept of short term memory (Lezak, 1995) and is often considered pivotal to other "Executive Functions" as its contribution to the processes subsumed under this term is fundamental. Experimental research and functional imaging confirm that the pre-

frontal cortex (PFC) plays a strong role in the different components of WM (Romanski, 2004).

1.7.2.1 Visual/Spatial Working Memory

Different models have stimulated research into WM. One of the most influential of these is that suggested by Baddeley and Hitch. This model will be used in this review to aid the understanding of the deficits in WM that are commonly reported in PD. According to the model of WM suggested by Baddeley and colleagues (Baddeley, 2003b; Baddeley & Della Sala, 1996; Baddeley & Hitch, 1974; Fuster, 2001), the visuo-spatial component may be conceptualised as the ability to temporarily store and manipulate visual (colour, shape) or spatial (location) characteristics of objects. As can be seen in Table 6, a wide range of tests and experimental tasks have been employed to examine this area of functioning in PD. Tasks often vary in the complexity and processing demands required for their successful completion, and this may explain some of the inconsistent findings in this literature.

Table 6: Tasks used for assessing visual/spatial working memory deficits for individuals with Parkinson's disease.

Authors	Test/Experimental task	Task Requirement	Impairment Found
Boller et al., (1998)	Corsi Cubes	Simple storage	Yes [a]
Bradley et al., (1989)[study 1]	Spatial span*	Simple storage	No
Bradley et al.,(1989)[study 1]	Complex spatial span*	Manipulation/interference	Yes
Costa et al., (2003)	n-back Visual object *	Distraction	Yes [c]
	Visual spatial*	Distraction	No [c]
Fournet et al., (1996)	Spatial span task*	Delay/interference	Yes
Fornet et al., (2000)	Spatial span task*	Simple storage/ Delay/interference	Yes [c]
Kemps et al., (2005)	Corsi Blocks	Simple storage	Yes
Le Bras et al., (1999)	Pattern span task*	Manipulation	Yes
Morris et al., (1988)	Corsi Blocks *	Simple storage	No
Owen et al., (1992)	Corsi cubes*	Simple storage	No/Yes [b, c]
	Self ordered search task/spatial*	Self directed search	Yes [b]
Owen et al., (1993)	Self ordered search task/spatial*	Self directed search	Yes [b]
Owen et al., (1997)	Self ordered search task/spatial*	Self directed search	Yes [b]
	Self ordered search task/visual*	Self directed search	Yes [b]
Postle et al., (1997)	Spatial WM task*	Delay	Yes
	Object WM task*	Delay	No
Stepanokava & Ruzicka (1998)	Spatial WM task	Recall/Recognition	No
Stofferes et al., (1997)	Corsi Blocks*	Simple storage	Yes [c]
Sullivan et al., (1993)	Corsi Blocks	Simple storage	No
	Corsi Blocks	Distraction	No
Tamura et al., (2003)	Spatial span (WMS-R)	Simple storage	No
	Spatial span Backward (WMS-R)	Manipulation	No

[a] Groups divided in terms of levels of depressive symptoms; [b] Groups divided in terms of severity of motor symptoms;[c] Groups tested on and off medication;* Computer generated task

1.7.2.2 Simple Storage/ Delay Tasks

Simple storage of information requires fewer resources than active manipulation, therefore a relative preservation of this skill might be expected in the early stage of PD. Simple storage for spatial WM has frequently been assessed using a variation of the Corsi blocks task (see Table 6). Preserved simple storage of visuo-spatial material for PD patients with mild to moderate symptoms relative to healthy controls, has been reported by a number of authors (Bradley, Welch, & Dick, 1989; Morris et al., 1988; Sullivan, Sagar, Cooper, & Jordan, 1993; Tamura, Kikuchi, Otsuki, Kitagawa, & Tashiro, 2003), regardless of depressive symptoms (Boller, Marcie, Starkstein, & Traykov, 1998). However, while there are exceptions to this finding, it is considered that these inconsistencies are likely to reflect differences in task complexity or subject characteristics (Kemps, Szmalec, Vandierendonck, & Crevits, 2005; Stoffers, Berendse, Deijen, & Wolters, 2003).

1.7.2.3 Complex Visuospatial Working Memory Tasks

It might be expected that visuo-spatial impairments would be more pronounced if a task required active manipulation of material rather than simple maintenance, further, that any delays or distractions would produce a greater level of difficulty. However, as with simple span tasks, deficits are consistently found for medicated patients with mild to moderate symptoms (Baddeley & Della Sala, 1996; Fournet, Moreaud, Roulin, Naegele, & Pellat, 1996, , 2000; Le Bras, Pillon, Damier, & Dubois, 1999), with no significant impairment in non-medicated patients at the early stage of PD (Owen et al., 1993a; Owen, Iddon, Hodges, Summers, & Robbins, 1997; Owen et al., 1992). One study has reported a finding contrary to this pattern. Owen et al., (1995) reported deficits in a spatial sequence generation task only in a

non-medicated group, and not in the medicated PD groups with mild or severe motor problems (Owen, Sahakian, Hodges, Summers, & et al., 1995).

Surprisingly, the addition of interference or delay does not differentially affect PD patients relative to controls, with similar decrements in performance being evident as task difficulty increases (Fournet, Moreaud, Roulin, Naegele, & Pellat, 2000; Le Bras, Pillon, Damier, & Dubois, 1999; Sullivan, Sagar, Cooper, & Jordan, 1993).

In an additional refinement, Postle et al. (1997) tested and confirmed their hypothesis that structures supporting WM may be differentially affected by the disease pathology associated with early PD. Therefore, WM for features and objects, mediated by the ventrolateral prefrontal cortex, should remain relatively unimpaired, while visual spatial WM, mediated by the dorsolateral pre-frontal cortex, should be a more sensitive measure of impairment as this structure would deteriorate earlier in the disease process. However, Costa et al. (2003) reported the opposite effect when comparing outcomes for an n-back[1] visual object and visual spatial WM task. While patients performed with normal accuracy in the visual-spatial WM task, they showed significant impairments for performance on the visual-object WM task. These authors suggest that the visual object task used in their study may have been more difficult than that used in other studies, thereby creating longer latencies and reduced accuracy in response selection (Costa et al., 2003).

Neither of these findings were supported by Owen, (1997b) who, using a self-ordered search task, examined the effects of organisational strategy on spatial and object WM at different stages of PD. Patients were divided into groups according to

[1] The n-back task is an experimental task where the participant is presented with a series of stimuli either visual or auditory and are required to indicate whether the current stimulus matches a stimulus presented n-back in the series where n= a number between 0-3.

disease severity, early course of the disease, medicated with mild-moderate physical symptoms, and medicated with severe physical symptoms. Non-medicated patients in the early course of the disease were not significantly different from controls, while medicated patients with mild and severe motor symptoms made significantly more search errors for both visual object and spatial task (Owen et al., 1993a; Owen, Iddon, Hodges, Summers, & Robbins, 1997; Owen et al., 1992).

Stepanokova and Ruzicka (1998) have suggested that many of the tests used to assess visuo-spatial WM are unusual or novel, creating greater task demands. Therefore, these authors used tasks that more closely resembled everyday problems and reported no deficits in visuo-spatial functioning for patients with PD compared to controls (Stepankova & Ruzicka, 1998).

1.7.2.4 Summary

Despite the different methodologies used in the studies reviewed, a consistent pattern emerged from the literature, with visuo-spatial WM deficits being apparent even in the early course of the disease process for medicated PD patients. On the other hand, there appears to be consistent evidence of spared visuo-spatial WM for early stage non-medicated patients. Furthermore, the addition of a delay or interference does not differentially impair the performance of PD patients. There was no clear support for the assertion that visuo-spatial WM deficits are evident for tasks that require active manipulation while not evident with simple storage tasks, or for the assertion that spatial tasks are more likely to show deficits than object WM tasks.

1.7.2.5 Verbal Working Memory

According to Baddeley's model, the second subcomponent of the WM system is the phonological loop which holds verbal information in a phonological code, whether presented visually or verbally. The phonological loop can be further divided into a temporary store that can only hold the memory trace for a few seconds if the information is not rehearsed, and the sub-vocal rehearsal system (Baddeley, 2003b). The subvocal rehearsal system not only enables information to be maintained, it is also the process by which information entering the system in a non-verbal form is coded. The memory span for verbal information is defined as the amount of material that can be actively stored in the rehearsal loop and subsequently articulated. Two phenomena that are known to reliably influence the verbal span are the word length effect (word spans decrease as the length of the words to be recalled increases) and the phonological similarity effect (i.e. words that are phonologically similar are more difficult to remember Baddeley, (2003b)).

1.7.2.6 Simple Storage and Delay

For patients with PD, it has been suggested that verbal WM may be less vulnerable to impairment at the earlier stages of the disease process than visuospatial WM (Lewis et al., 2003). Indeed, as noted by Lewis et al. (2005), spatial WM deficits may occur while verbal WM remains unimpaired within the same patient group (Bradley, Welch, & Dick, 1989; Owen, Iddon, Hodges, Summers, & Robbins, 1997). While this observation adds weight to the suggestion that spatial WM may be more vulnerable than Verbal WM, it is not unequivocal as the opposite pattern has also been reported (Tamaru, 1997).

However, as can be seen in Table 7, at least in terms of simple storage, the performance of PD patients relative to controls has consistently been found to be unimpaired. Intact verbal WM has been a robust finding, regardless of depressive symptoms (Boller, Marcie, Starkstein, & Traykov, 1998), or disease severity (Graceffa, Carlesimo, Peppe, & Caltagirone, 1999; Sullivan, Sagar, Cooper, & Jordan, 1993).

One notable exception to these findings is a study by Press et al. (2002). In this study, participants were presented with a Sternberg item recognition paradigm with memory sets of one, three, or five digits. Following this, they were presented with a probe and asked to indicate (by pressing a key) whether or not it was part of the memory set. While there was no effect for accuracy or reaction time as a result of dopaminergic state, patients with PD showed evidence of impaired reaction time and accuracy in higher WM load conditions relative to controls. Interestingly, these impairments were only evident on the first session and patients with PD were as accurate as controls by the second session. The authors suggest that a procedural learning deficit may explain impairments in WM performance for PD patients. A unique feature of this study was that it required recognition rather than recall, which is generally regarded as less memorially demanding. However, while no specific delay is imposed, the Sternberg item recognition paradigm automatically imposes a delay. Therefore, the characteristics of this test may be more complex than those required by a simple storage paradigm, and may explain the apparent discrepancy.

Table 7: Tasks used for assessing verbal working memory deficits in individuals with Parkinson's disease.

Authors	Test/Experimental task	Task Requirement	Impairment
Boller et al. (1998)	Digit span	Simple storage	No [a]
Bradley et al. (1989) study 1	Digit span *	Simple storage	No
Bradley et al.,(1989) study 2	Memorising short phases *	Decision making/ interference	No No
Bublak et al.. (2002)	Digit span	Simple storage	No
	Digit Backward	Manipulation	No
	Digit Ordering	Manipulation	Yes
	Reading span task	Distraction	Yes
	Number reordering*	Manipulation	Yes
Cooper et al. (1991)	Digits forward	Simple storage	No
	Digits Backward	Manipulation	Yes
	Digit ordering	Manipulation	Yes
Cox (2002)	Counting task	Distraction	Yes
Dalrymple-Alford et al. (1996)	Digit span	Simple storage	No
Fournet et al. (1996)	Word span *	Delay	Yes
Fournet et al. (2000)	Word span*	Delay	Yes [c]
Gabrieli et al. (1996)	Reading span	Distraction	Yes
	Arithmetic span	Distraction	Yes
Gilbert et al. (2005)	Digit span	Simple storage	No
	Verbal span	Manipulation	Yes
Graceffa et al. (1999)	Word span	Simple storage	No
	Brown Peterson distracter task*	Delay	No
Kensinger et al. (2003)	Digit span	Simple storage	No
	Word span	Simple storage	No
	N-back task*	Distraction	Yes
	Reading span	Distraction	Yes
Lewis et al. (2003)	Number span	Simple storage	No [d]
	Computer generated number re-ordering*	Manipulation	Yes [d]
Lewis et al. (2005)	Number span*	Delay	No [c]
	number re-ordering*	Manipulation	No/Yes [c]
Moreaud et al. (1997)	Word span*	Delay	Yes
Owen et al. (1997)	Computerised verbal working memory*	Organisational strategy	No/Yes [b]
Press et al. (2002)	Item recognition*	Simple storage	Yes [c]
Skeel et al. (2001)	Word span	Simple storage	No [c]
	Word span	Delay/Interference	No [c]
Stebbins et al. (1999)	Listening span test	Distraction	Yes
	Digit ordering test	Manipulation	Yes
Sullivan et al. (1993)	Letter recall	Simple storage	No
		Distraction	Yes
Tamura et al. (2003)	Digit span	Simple storage	No
	Digit span/backwards	Manipulation	Yes
	Mental calculation	Manipulation	Yes

[a] Groups divided in terms of levels of depressive symptoms; [b] Groups divided in terms of severity of motor symptoms;[c] Groups tested on and off medication; [d] Groups divided in terms of cognitive ability; * Computer generated task

The inclusion of a delay would be expected to add an additional load to the WM, and as can be seen from Table 7, with few exceptions the PD patients are impaired compared to controls when the WM task has a delay component (Bublak, Muller, Gron, Reuter, & von Cramon, 2002; Fournet, Moreaud, Roulin, Naegele, & Pellat, 1996, , 2000; Lewis et al., 2005).

However, the imposition of a delay does not appear to simply reflect an inefficient processing skill. If this were the case, an increase in the delay period would differentially affect PD patients compared with controls. But both patients with PD and controls are equally affected by increases in the delay period (Fournet, Moreaud, Roulin, Naegele, & Pellat, 2000). This has been found for patients both on and off medication (Cooper, Sagar, Jordan, Harvey, & Sullivan, 1991; Fournet, Moreaud, Roulin, Naegele, & Pellat, 2000).

Furthermore, the introduction of simple distraction tasks do not differentially affect patients with PD (Cooper, Sagar, Jordan, Harvey, & Sullivan, 1991; Fournet, Moreaud, Roulin, Naegele, & Pellat, 1996). Moreover, in both simple span tasks and tasks that introduce a delay, patients with PD have not been found to be differentially affected by the word length effect or phonological similarity effect when compared with controls (Graceffa, Carlesimo, Peppe, & Caltagirone, 1999; Moreaud, Fournet, Roulin, Naegele, & Pellat, 1997).

1.7.2.7 Complex Verbal Working Memory Tasks

As can be seen from Table 7, deficits are more likely when active manipulation of material is required, rather than simple maintenance. In studies that used the same patient group to examine both tasks of simple storage and manipulation, a consistent pattern of spared simple storage and impaired manipulation

was found (Bublak, Muller, Gron, Reuter, & von Cramon, 2002; Cooper, Sagar, Jordan, Harvey, & Sullivan, 1991; Gilbert, Belleville, Bherer, & Chouinard, 2005; Kensinger, Shearer, Locascio, Growdon, & Corkin, 2003; Lewis et al., 2003; Sullivan, Sagar, Cooper, & Jordan, 1993; Tamaru, 1997). However, there were some exceptions to this pattern of deficits (Bradley, Welch, & Dick, 1989; Lewis, Slabosz, Robbins, Barker, & Owen, 2005).

All the previously mentioned studies have combined patients with different levels of disease severity. In contrast, using a task that required organisational strategy, Owen et al. (1997) reported that when patients were divided into groups according to disease severity, those in the early course of the disease (mean = 18 months) and those medicated with mild-moderate physical symptoms demonstrated no verbal WM impairments. However, the group of medicated patients with severe physical symptoms did show impairment.

1.7.2.8 Summary

The research reviewed here consistently found evidence of preserved simple storage for verbal WM in patients with PD. Deficits were more likely to be reported for tasks that required a delay or active manipulation of the material presented. Neither word length effect, phonological similarities effect, nor the length of a delay differentially impaired patients with PD relative to controls. Further, there was some evidence that even complex verbal WM tasks were preserved for early stage medicated and non-medicated patients with PD. The literature reviewed here provides some tentative support for the assertion that the phonological loop is less vulnerable to impairments associated with PD than the visuo-spatial sketch pad. The variation in performance over different task demands may be attributable to the

different regions of the brain that are activated during these tasks. MRI studies have demonstrated that low load non-spatial WM task activate the left ventral lateral prefrontal cortex, while high load tasks activate the dorsolateral prefrontal cortex.

1.7.3 Planning

Planning refers to the ability to reach a desired goal through a number of intermediary steps, some of which may be counter-intuitive in that they do not lead directly to the end goal (Owen, 1997a). The prefrontal cortex is thought to play a major role in planning ability (Owen, 1997a) and findings from patients with frontal lobe lesions (Carlin et al., 2000; Owen, Downes, Sahakian, Polkey, & Robbins, 1990) and imaging studies have supported this association (Baker et al., 1996; Cools, Stefanova, Barker, Robbins, & Owen, 2002; Owen et al., 1992). Deficits attributed to planning ability have been reported in patients with PD using the Modified Six Elements Task (from the Behavioral Assessment of the Dysexecutive Syndrome test battery) (Uekermann et al., 2004), and variations of the Tower of London task (Cools, Stefanova, Barker, Robbins, & Owen, 2002; Culbertson, Moberg, Duda, Stern, & Weintraub, 2004; Morris et al., 1988; Owen et al., 1992). Evidence of planning deficits have been found in the early stages of the disease process. For example, in a study conducted by Owen et al.(1992) which used three groups, early non-medicated, mild to moderate stage medicated, and late stage medicated, patients with PD spent a longer time planning solutions, compared with controls. Furthermore, increased errors in execution of solutions were evident for patients in the later stages of the disease. However, goal-sub-goal conflicts which are attributed to a failure to inhibit a pre-potent response rather than planning deficits, has been offered as an alternative

explanation for the difficulties reported for patients with PD using the Tower tasks (Goel & Grafman, 1995).

1.7.4 Attention

There are conflicting findings in the literature as to whether patients with PD demonstrate deficits in attention. This may be due to the variety of neuropsychological tests that have been used to assess this area, including digit span and the Wisconsin Card Sorting Test (WCST). A major theory that has driven much of the research on this topic suggests that deficits in patients with PD are a result of reduced attentional resources. Brown and Marsden (1991) have suggested a model (based on that proposed by Shallice), of a supervisory attention system (SAS). In this model, attention must be consciously allocated in novel or demanding tasks that cannot be performed automatically. The SAS is considered to have limited capacity and impairments in performance will be observed when this is exceeded. Indeed, it has been repeatedly demonstrated that people with PD have greater difficulty when asked to perform two tasks simultaneously (dual task tests) that exceed their attentional capacity (Brown & Marsden, 1988; Dalrymple-Alford, Kalders, Jones, & Watson, 1994). Therefore, deficits might not be apparent at easier stages of a given task and only become apparent as the task increases in difficulty (Brown & Marsden, 1991). Further, tasks that require internally generated cues will be more effortful (e.g., more complex aspects of the Stroop task and tests such as the WCST). A number of studies have reported findings that support this theory (Cooper & Sagar, 1993; Dujardin, Degreef, Rogelet, Defebvre, & Destee, 1999).

Much of the research regarding attention has concentrated on attentional set shifting, namely, the ability to flexibly change behaviour in response to changing

contingencies of a task and requiring the ability to shift attention to relevant stimuli. Imaging studies suggest that efficient performance of attentional set-shifting is associated with both fronto-striatal functioning and the integrity of the frontal lobe (Marie et al., 1999; Monchi et al., 2004; Monchi, Petrides, Petre, Worsley, & Dagher, 2001). Attentional set-shifting difficulties have commonly been reported in patients with frontal lobe damage and patients with PD using a variety of tasks including the Odd Man Out Task (Flowers & Robertson, 1985; Richards, Cote, & Stern, 1993), intra-and-extra dimensional shift paradigms (Gauntlett-Gilbert, Roberts, & Brown, 1999; Lewis, Slabosz, Robbins, Barker, & Owen, 2005; Owen et al., 1992; Owen et al., 1993b), verbal fluency (Zec et al., 1999), the Stroop test (Dujardin, Degreef, Rogelet, Defebvre, & Destee, 1999), the California Card Sorting Test (Dimitrov, Grafman, Soares, & Clark, 1999), and the Wisconsin Card Sorting test (Bondi, Kaszniak, Bayles, & Vance, 1993b; Canavan et al., 1989; Farina et al., 2000; Inzelberg et al., 2001). However, Owen et al. (1993) suggest that the fundamental deficit in attentional set-shifting for the frontal lobe and PD patients may be due to different cognitive processes. While PD patients have difficulty shifting attention to a new, previously irrelevant dimension ("learned irrelevance"), patients with frontal lobe damage tend to continue to attend to a previously relevant, but now irrelevant dimension (perseveration). However, van Spaendonck et al., (1995) reported that deficits for patients with PD were only apparent when they were first required to shift set, with no difference for subsequent attentional set shifting. Others have suggested that set-shifting deficits appear only when patients with PD are required to rely on internally-generated cues and are unimpaired when external cues are provided (Brown & Marsden, 1988; Hsieh, Lee, & Tai, 1995). Deficits in set-shifting have been reported for patients during the early and late stage of the disease (Owen et al., 1992)

for both medicated (Canavan et al., 1989; Taylor, Saint-Cyr, & Lang, 1986) and non-medicated patients with PD (Canavan et al., 1989). Furthermore, deficits are not always ameliorated by dopamine, as shown by Lewis et al. (2005) who found no improvement in performance when patients were tested on L-dopa.

While tasks such as the WCST have frequently been used to test for deficits in attentional set-shifting, it has been noted that multiple cognitive skills in addition to a set-shifting requirement are required for effective completion. These include ability to stay on task, concept formation, and rule learning, making it difficult to analyse whether any reported deficits are indeed related to deficits in set-shifting or some other component (Rogers et al., 1998; Royall et al., 2002). To date, deficits in performance for patients with PD using WCST have been attributed to difficulties with forming, holding or shifting attention between sets. To more specifically investigate attentional set-shifting, tasks that deemphasised rule learning and concept formation have been used. Using these tasks, patients with PD still exhibit attentional set-shifting deficits when compared with age matched controls, even in the early stages of the disease process (Cools, Barker, Sahakian, & Robbins, 2001b; Rogers et al., 1998).

However, some aspects of attention appear to remain intact. The digit span test is generally considered to be a test of sustained attention. Patients with PD have consistently been reported as being unimpaired in this task (Boller, Marcie, Starkstein, & Traykov, 1998) regardless of disease severity (Graceffa, Carlesimo, Peppe, & Caltagirone, 1999; Sullivan, Sagar, Cooper, & Jordan, 1993).

1.7.5 Verbal Fluency

Extensive research has been generated regarding fluency tasks and PD. Semantic and phonemic categories are generally used to test deficits in this skill. However, some research has focused on production of verbs (as opposed to nouns) as it has been suggested that the retrieval of action words relies more heavily on the prefrontal cortex (Piatt, Fields, Paolo, Koller, & Troster, 1999; Piatt, Fields, Paolo, & Troster, 1999; Woods, Carey, Troster, & Grant, 2005). Nonetheless, outcomes using semantic and phonemic categories have been inconsistent with some researchers reporting deficits for verbal fluency tasks while others have reported no such deficits (see Table 8).

A number of explanations have been offered for these disparate findings. For example, Hanley et al. (1990) indicated that group characteristics and suitable control groups were important, reporting that the semantic and letter deficit observed in their study disappeared when age, current verbal ability, and depression were taken into account. The sensitivity of the word-fluency measure used may affect the outcomes. Generating words from a semantic category may be more effortful than from a phonemic category, and therefore provide a more sensitive measure (Auriacombe et al., 1993). Indeed, deficits in semantic fluency have been reported in groups where phonemic fluency has been preserved (Auriacombe et al., 1993; Raskin, Sliwinski, & Borod, 1992; Zec et al., 1999).

Table 8: Examples of studies that have found contradictory findings for Phonemic and Semantic Verbal Fluency Tasks.

Type of Deficit	Authors
Present	
Phonemic	(Azuma, Cruz, Bayles, Tomoeda, & Montgomery, 2003; Bayles, Trosset, Tomoeda, Montgomery, & Wilson, 1993; Gurd & Ward, 1989)
Semantic	(Auriacombe et al., 1993; Azuma, Cruz, Bayles, Tomoeda, & Montgomery, 2003; Bayles, Trosset, Tomoeda, Montgomery, & Wilson, 1993; Gurd & Ward, 1989; Randolph, Braun, Goldberg, & Chase, 1993; Raskin, Sliwinski, & Borod, 1992)
Absent	
Phonemic	(Azuma et al., 1997; Downes, Sharp, Costall, Sagar, & Howe, 1993; Gotham, Brown, & Marsden, 1988; Hanley, Dewick, Davies, Playfer, & Turnbull, 1990; Piatt, Fields, Paolo, & Troster, 1999; Raskin, Sliwinski, & Borod, 1992; Troster et al., 1998; Van Spaendonck, Berger, Horstink, Buytenhuijs, & Cools, 1996)
Semantic	(Azuma et al., 1997; Downes, Sharp, Costall, Sagar, & Howe, 1993; Gotham, Brown, & Marsden, 1988; Hanley, Dewick, Davies, Playfer, & Turnbull, 1990; Troster et al., 1998; Zec et al., 1999)

In the study conducted by Auriacombe et al. (1993), semantic deficits were found in the absence of letter fluency deficits. These authors suggest that the letter provided in letter fluency tasks provided a stronger prompt than a semantic category, which would therefore rely more heavily on the individual's spontaneous ability to

retrieve the information. This hypothesis was further examined by Randolph et al. (1993), who tested patients with Alzheimer's disease (AD) and PD using a cued and uncued semantic fluency task. In the uncued task, participants were asked to provide as many different exemplars from a semantic category in the standard way. However, for the cued task, participants were provided with a cue every 15 seconds, (e.g., if the semantic category was "animals" a cue at 15 seconds might be animals you find in the home). Patients with PD performed significantly worse than healthy elderly controls only in uncued conditions. On the other hand, patients with AD did not benefit from cues, indicating reduced semantic stores. However, Azuma et al. (1997) proposed that not all semantic and letter categories were equivalent, and that differential performance on these two tasks was also likely to be influenced by the relative difficulty of individual categories used by different researchers.

Alternating word categories have been used to increase the sensitivity of verbal fluency tasks. Zec et al. (1999) reported preserved phonemic word fluency with impaired semantic and alternating word fluency. However, Gotham, Brown and Marsden (1988) reported evidence of deficits with alternate word fluency tasks only when the patients with PD were tested when off L-Dopa. Moreover, Downes et al. (1993) reported that the deficits in verbal fluency tasks were not attributable to basic fluency or switching deficits, as patients with PD were able to shift between probes for the same domain (e.g. phonemic-phonemic, semantic-semantic), and that deficits only appeared when the participants had to switch between domains (e.g phonemic – semantic).

In a recent meta-analysis of 68 studies of verbal fluency deficits, Henry et al. (2004) found that both phonemic and semantic fluency were impaired for PD patients.

However, sematic fluency tasks were relatively more impaired than phonemic fluency tasks. Moreover, tests that required switching were differentially impaired. This meta analysis lends support to the assertion that not all verbal fluency tasks are equally sensitive, and some care needs to be exercised when selecting which task to use (Henry & Crawford, 2004).

1.8 Language and Verbal Functions

The most noticeable communication deficits in patients with PD are those associated with motor dysfunctions, and include hypophonia and hyperkinetic dysarthria (difficulty with speech mechanisms, Murdoch, 2001). However, there is increasing evidence that basal ganglia are also implicated in complex language processes and verbal function (Murdoch, 2001). Given this association, it is not surprising that deficits in complex language and verbal functions have been reported in patients with PD (Azuma et al., 1997; Gotham, Brown, & Marsden, 1988; Grossman et al., 1991; Grossman, Carvell, Stern, Gollomp, & Hurtig, 1992; Natsopoulos et al., 1991).

1.8.1 Complex Language

Impairments in many different aspects of complex language have been associated with PD, including sentence comprehension and pragmatics of speech (rules for appropriate social language), difficulties with interpreting ambiguity, figurative language, and confrontational naming (Godbout & Doyon, 2000; Grossman, 1999; Grossman et al., 1991; Grossman, Carvell, Stern, Gollomp, & Hurtig, 1992; Lewis, Lapointe, Murdoch, & Chenery, 1998; Murdoch, 2001). Deficits in complex language have been attributed to grammatical difficulties (Natsopoulos et al., 1991), slowed information processing speed (Grossman et al.,

2002), and working memory deficits associated with PD (Baddeley, 2003a; Howard, Binks, Moore, & Playfer, 2000). There is also evidence that pragmatic social communication skills such as topic maintaince and appropriate interpretation of information are impaired for individuals with PD (McNamara & Durso, 2003). Pragmatic and social deficits are overtly evident in patients with PD in terms of their physical presentation e.g., flat affect and lack of body language.

1.9 Visuoperception/Visuospatial Functions

Deficits in visuoperceptual/visuospatial functions have commonly been reported for patients with PD even in the earliest stages of the disease process, even when the task requires no motor components (Hovestadt, de Jong, & Meerwaldt, 1987). These deficits have been associated with lesions in the right posterior cortex (Lezak, 1995; Treccani, Torri, & Cubelli, 2005). Impairments in patients with PD have been reported using a variety of tasks (for a full listing and review of tests used with PD patients see Waterfall & Crowe, 1995). Some of the more common tests used are: Judgement of Line Orientation (Montse, Pere, Carme, Francesc, & Eduardo, 2001), mental rotation tests (Crucian et al., 2003; Lee, Harris, & Calvert, 1998), the Rey Osterrieth Complex Figure Test (Freeman et al., 2000; Grossman et al., 1993), Bicycle Drawing Test (Sandyk, 1994), and Cube Copying task (Maeshima, Itakura, Nakagawa, Nakai, & Komai, 1997).

Performance on visuoperceptual/visuospatial tasks has been reported as showing a pattern of deterioration over time that is not significantly related to motor deficits (Katsarou et al., 1998), but that is correlated with the onset of symptoms associated with dementia (Levin et al., 1991; Raskin et al., 1990).

However, some authors have argued against the proposition that PD is associated with a generalised visuoperceptual/visuospatial deficit, suggesting instead that differences result from methodological issues such as task requirements. For example, many earlier studies used timed tasks (Brown & Marsden, 1986; Waterfall & Crowe, 1995). Furthermore, as has been pointed out by Crucian and Okun (2003), visuoperceptual/visuospatial tasks require multiple cognitive processes such as attentional resources and working memory, and these factors may underlie any observed deficits. This suggestion has been supported by Waterfall and Crowe (1995), who in a recent meta-analysis showed that visuoperceptual/visuospatial tasks vary greatly in their requirements and can be further reduced to a number of different categories. These authors reported that deficits are more likely to be seen in complex, higher order tasks that require attention, problem solving and internal control of behaviour, and not in lower order tasks with externally generated cues.

Deficits in executive skills have been particularly implicated in visuoperceptual/visuospatial functioning (Bondi, Kaszniak, Bayles, & Vance, 1993a; Crucian et al., 2003; Crucian & Okun, 2003). However, this finding is not conclusive as other authors have reported no association (Cronin-Golomb & Braun, 1997). These conflicting results indicate that the relationship between executive and visuoperceptual/visuospatial functions is complex and multifactorial.

1.10 Memory and Learning

Deficits in memory have been frequently reported for patients with PD (Stefanova et al., 2001). It has generally been accepted that while cued and recognition memory appear to be unimpaired (suggesting intact coding ability), patients with PD have difficulty with the more effortful task of free recall, thereby

indicating a deficit in retrieval of the information. (Brown & Marsden, 1988, , 1991; Buytenhuijs et al., 1994; Crucian et al., 2003; Crucian & Okun, 2003; Hsieh & Lee, 1999; Knoke, Taylor, & Saint-Cyr, 1998; Sagar, Sullivan, Gabrieli, Corkin, & Growdon, 1988). However, a recent review of the literature has challenged the view that recognition memory remains intact for patients with PD (Whittington, Podd, & Kan, 2000). Whittington et al. (2000) conducted a meta analytical review of the literature and found that while recognition memory remained unimpaired in de novo patients, there was a small recognition deficit for medicated patients with PD (Whittington, Podd, & Kan, 2000). Further, greater deficits in recognition memory were found with increased task difficulty (Whittington, Podd, & Kan, 2000). Also, it has been reported that while patients with PD show deficits in recognition over short delays, this is ameliorated after a longer delay (Cooper, Sagar, & Sullivan, 1993). Of the executive function measures, working memory has been reported as most predictive of deficits, with a strong relationship between working memory and recall of information (Gabrieli, Singh, Stebbins, & Goetz, 1996; Higginson et al., 2003). While patients with PD spontaneously recall less information, their ability to learn new information and their rate of forgetting is not significantly different to that of healthy controls (Buytenhuijs et al., 1994; Stefanova, Kostic, Ziropadja, Ocic, & Markovic, 2001).

1.11 Psychiatric and Behavioural Symptoms

1.11.1 Overview

There are a number of psychiatric and behavioural symptoms associated with PD that may be as debilitating as the cognitive and motor symptoms, and are often associated with reduced quality of life and caregiver distress (Caap-Ahlgren &

Dehlin, 2001; Marsh, 2000). The most common non-motor symptoms are listed in Table 9. It is likely that psychiatric symptoms may interact to exacerbate cognitive and motor problems associated with PD, making them an important consideration when assessing cognitive deficits. Therefore, a brief overview of the commonly co-morbid non-motor symptoms is provided here.

Table 9: Common psychiatric and other non-motor symptoms that are associated with Parkinson's disease (Dewey, 2003).

Depression	Sleep disorders
Anxiety	Olfactory dysfunction
Psychosis	Pain and sensory disturbance
Fatigue	Seborrhea
Apathy	Autonomic dysfunction
Dementia	Visual disturbance

While hallucinations and psychosis are considered to be common side effects of medications used to control motor symptoms (Marsh, 2000), other non motor symptoms (e.g., depression, anxiety, apathy and fatigue) are reported by over 80% of patients with PD (Marsh, 2000; Shulman, Taback, Bean, & Weiner, 2001). Accurate identification of these disorders may be difficult as many symptoms associated with depression, anxiety, apathy and fatigue overlap with PD symptoms. However, it has been consistently demonstrated that psychiatric disorders are more common in PD patients than in age-matched controls.

1.11.2 Depression

Depression refers to a state of low mood characterised by feelings of inadequacy, inactivity, and pessimism about the future. Depression is one of the most common non motor symptoms associated with PD, with reported prevalence ranging from 7-76% (Slaughter, Slaughter, Nichols, Holmes, & Martens, 2001; Veazey, Aki, Cook, Lai, & Kunik, 2005). The reported variation is due mostly to differences in sampling methods, type of assessment scales used, variations in cut-off points for scales, and how depression is actually defined (Slaughter, Slaughter, Nichols, Holmes, & Martens, 2001; Veazey, Aki, Cook, Lai, & Kunik, 2005). It has been suggested that a true rate of around 31% would be found in community samples of patients with PD (Slaughter, Slaughter, Nichols, Holmes, & Martens, 2001; Veazey, Aki, Cook, Lai, & Kunik, 2005). However, it is likely that depression associated with PD is under-diagnosed as many of the symptoms associated with PD are similar to those of low mood (e.g. difficulties sleeping, psychomotor retardation and apathy) and may be overlooked (McDonald, Richard, & DeLong, 2003; Shulman, Taback, Rabinstein, & Weiner, 2002).

There is some debate in the literature as to whether depressive symptoms are secondary, resulting from being diagnosed with a debilitating disorder, or are associated with neuropathological changes that accompany the disorder. The occurrence of depression in PD is reported as having a bimodal distribution, being more frequent in early and late stages of the disease, consistent with the assertion that it is a reactive depression. However, changes in mood often predate the diagnosis of PD, and are ameliorated with medication (Leentjens, 2004; Shiba et al., 2000). Furthermore, as indicated previously, the noradrenaline and serotonergic pathways

implicated in depression in the general population are compromised in patients with PD (McDonald, Richard, & DeLong, 2003; Murai et al., 2001). It is likely that a diagnosis of PD and neuropathological changes interact together with the individual's personality to increase the risk of low mood, which may sometimes be severe enough to warrant a diagnosis of major depressive episode. Regardless of the exact etiology, mood disorders are commonly co-morbid in patients with PD, and are associated with difficulties in concentration and attention, and impact on an individual's performance on a range of cognitive tasks and everyday activities (Kuzis, Sabe, Tiberti, Leiguarda, & Starkstein, 1997).

1.11.3 Anxiety

Anxiety refers to feelings of fear, apprehension and dread about the future without a specific cause. Anxiety disorders occur in up to 40% of patients with PD, a rate which is higher than that found in other disease populations (Richard, Schiffer, & Kurlan, 1996; Walsh & Bennett, 2001). While a range of anxiety disorders have been reported as associated with PD symptoms, they are more commonly clustered in the generalized anxiety, panic and phobic disorder spectrum (Walsh & Bennett, 2001). Anxiety commonly occurs co-morbidly with depression, but may occur as an isolated cluster of symptoms (Walsh & Bennett, 2001).

As with depression, there is some debate as to whether the symptoms associated with anxiety that occur in patients with PD represent a psychological reaction to the disease, or are directly linked to neuropathalogical changes associated with the disease process. It has been suggested that anxiety could be a side effect of the L-dopa. However, at least in terms of panic attacks, symptoms occur almost exclusively in the "OFF" phase of fluctuations and are relieved by the administration

of Levodopa or dopaminergic agonists (Vazquez, Jimenez-Jimenez, Garcia-Ruiz, & Garcia-Urra, 1993). Furthermore, as with depressive symptoms, there is an increased occurrence of anxiety disorders that predates the diagnosis of PD (Shiba et al., 2000). Recent research suggests that the severity of anxiety symptoms is related to depletion of dopamine and noradrenaline in the locus coeruleus and areas of the limbic system (Remy, Doder, Lees, Turjanski, & Brooks, 2005).

1.11.4 Apathy

Apathy is defined as a lack of motivation, interest or concern, which manifests itself as a decrease in goal directed behaviour (Marin, 1990). Between 30-45% of patients with PD report symptoms consistent with this syndrome (Isella et al., 2002; Starkstein et al., 1992). Apathy is often co-morbid with depression (Starkstein et al., 1992), and may be mistaken for depression as a number of the symptoms overlap. However, apathy is considered a separate neuropsychiatric syndrome differentiated by the fact that, unlike depression, there is no low mood or feelings of hopelessness (Levy et al., 1998). Symptoms of bradyphrenia and bradykinesia are similar to those associated with apathy, and it has been suggested they result from neuropathological changes in the same subcortical structures (Marsh, 2000). It has been suggested that apathy results from dopaminergic nigro-striatal denervation (Levy & Dubois, 2005), and this is supported by the dopamine-dependent differences in severity that have been reported when patients are in the "on or off" state. With or without depression, apathy is significantly correlated with deficits on cognitive tasks, e.g., planning, initiation and monitoring of goal-directed behaviours (Levy et al., 1998; Schrag, 2004).

1.11.5 Fatigue

Fatigue is described as the sense of being overly tired, lacking energy and feelings of exhaustion, and is listed as a feature of anxiety and depression by the Diagnostic and statistical manual of mental disorders- Fourth edition (DSM-IV). Given symptom overlap with depression and anxiety, fatigue is often undiagnosed by physicians (Friedman & Chou, 2004). However, symptoms of fatigue, not explained by depression, have been reported in over 40% of individuals with PD. This contrasts with 4.5%-18% of the normal elderly reporting the same problems (Friedman & Chou, 2004; Karlsen, Larsen, Tandberg, & Jorgensen, 1999). Fatigue has been reported as the presenting symptom in 2% of patients with PD (Hoehn & Yahr, 1967), and many patients with PD rate fatigue as their most disabling symptom (Friedman & Friedman, 1993).

The neuropathological changes associated with fatigue are not well understood, but it is suggested that the symptoms may be related to dysfunction of the frontal lobes (Friedman & Chou, 2004). However, mental and physical symptoms may represent separate syndromes with different etiologies (Lou, Kearns, Oken, Sexton, & Nutt, 2001; Zenzola et al., 2003). This suggestion is supported by the finding that while other aspects of fatigue are influenced by depression, physical fatigue is not (Zenzola et al., 2003). Also, patients with PD report experiencing more physical fatigue than mental fatigue, and the severity of physical fatigue does not correlate with mental fatigue (Lou, Kearns, Oken, Sexton, & Nutt, 2001). Furthermore, while Levodopa has been helpful in treating physical fatigue associated with reduced activity, it does not ameliorate the symptoms of mental fatigue associated with reduced motivation.

1.11.6 Psychosis

Precise prevalence rates for psychosis are difficult to establish because of varying definitions used in the literature. However, hallucinations and delusions are relatively common in patients with PD, with prevalence rates of approximately 30% and 3% respectively (Ismail & Richard, 2004). The presentation of symptoms generally fall into two categories: patients who experience hallucinations but retain insight ("benign hallucinations"), and patients who experience hallucinations (typically without insight), and persecutory delusions in the context of dementia (Weintraub & Stern, 2005). The precise etiology of psychosis remains unclear, but it is generally accepted that they are related to an excess of dopaminergic medication (Ismail & Richard, 2004). While in some cases symptoms may predate medication, psychosis occurs at much lower rates in untreated patients with PD (Weintraub & Stern, 2005).

1.11.7 Sleep Disturbance

Sleep patterns change with age, and older individuals commonly have difficulty sleeping or require less sleep (Shochat, Loredo, & Ancoli-Israel, 2001). However, sleep disturbances are significantly more common in patients with PD than age-matched controls (Friedman & Chou, 2004). While sleep problems are varied, sleep fragmentation due to difficulties with sleep maintenance is the most common type of sleep disorder in PD (Friedman & Chou, 2004). Sleep disorders may be primary (i.e, directly related to PD) or secondary (i.e related to the side effects of medications, depression or anxiety). Primary problems that may interfere with sleep maintenance include difficulty turning in bed, respiratory problems, depression, anxiety and tremors. Secondary problems, related to the side effects of commonly

used medications, include the need for frequent urination and daytime sleepiness (Sanjiv et al., 2001).

1.11.8 Emotional Expression

Deficits in the ability to recognise emotional expression have been reported early in the disease process and PD patients have been reported as significantly impaired in their ability to decode primary facial expressions such as sadness, fear and disgust (Dujardin et al., 2004a; Kan, Kawamura, Hasegawa, Mochizuki, & Nakamura, 2002; Sprengelmeyer et al., 2003; Troisi et al., 2002; Yip, Lee, Ho, Tsang, & Li, 2003). These deficits do not appear to be influenced by clinical variables such as duration of illness, motor symptoms, or depression (Dujardin et al., 2004a; Yip, Lee, Ho, Tsang, & Li, 2003). Patients with PD also demonstrate emotional dysposity, the inability to vocally express feelings like anger, sadness, and verbal humour, and tend to produce monotonous flat speech (Benke, Bosch, & Andree, 1998).

However, impairments in the recognition or expression of emotions are not found with written or verbal stimuli (Kan, Kawamura, Hasegawa, Mochizuki, & Nakamura, 2002). The basal ganglia have been associated with the recognition of emotion (Cancelliere & Kertesz, 1990; Heilman & Gilmore, 1998; Weniger & Irle, 2002), and impairments have also been found following sub-thalamic nucleus stimulation (Dujardin et al., 2004b). As discussed previously, both these areas are implicated in PD, and their deterioration may explain difficulties with emotion recognition.

1.11.9 Dementia

Dementia is arguably the most severe psychiatric outcome associated with PD, representing multiple cognitive and /or behavioural deficits which result in a significant decline in the person's level of social or occupational functioning (using DSM-IV criteria). The reported prevalence for Parkinson's disease with dementia (PDD) varies greatly, largely due to methodological inconsistencies i.e., the way in which dementia is defined (Aarsland, Zaccai, & Brayne, 2005; Biggins et al., 1992; Mindham, 1999). However, it is generally accepted that prevalence rates of dementia among people with PD are much higher than in the general population i.e., approximately four to five times that of elderly individuals without PD (Aarsland, Andersen, Larsen, Lolk, & Kragh-Sorensen, 2003; Emre, 2003; Hobson & Meara, 2004; Mahieux et al., 1998). While the exact neurophysiological basis of PDD remains undetermined, progression to dementia has been found to be more likely in patients with longer disease duration, of older age, and with more severe motor symptoms (Biggins et al., 1992; Caparros-Lefebvre, Pecheux, Petit, Duhamel, & Petit, 1995; Hughes et al., 2000; Mahieux et al., 1998).

Research indicates that cognitive deficits characteristic of PDD differ from those associated with Alzheimer's disease (AD) (Mahieux et al., 1998; Stern et al., 1998). For example, while the initial symptom and essential characteristic of AD is impaired episodic memory, early executive function and visuospatial deficits are characteristic of PDD, with only mild impairments in memory retrieval being evident (Levy et al., 2002; Mahieux et al., 1998).

The focus of more recent research has been to determine the exact nature of baseline tests that are predictive of later PDD. Deficits in executive functions have

been reported by a number of authors (Azuma, Cruz, Bayles, Tomoeda, & Montgomery, 2003; Jacobs et al., 1995; Janvin, Aarsland, & Larsen, 2005; Mahieux et al., 1998; Woods & Troster, 2003). However, it is difficult to compare these studies because definitions of executive function vary (Salthouse, 2005). Nonetheless, from the research to date, it seems evident that PDD differs from AD, with a hallmark feature being executive dysfunction rather than a deficit in episodic memory. Moreover, executive dysfunctions appear to be an early indicator of later PDD.

1.11.10 Conclusions

It is clear that many patients with PD experience non-motor symptoms. Evidence of clinically significant mood, anxiety, and sleep disorders, along with fatigue, psychosis and apathy are frequently reported, and many patients with PD experience multiple symptoms. Perhaps the most debilitating of the psychiatric disorders associated with PD is dementia, which is characterised by a cluster of both cognitive and behavioural deficits.

1.12 Interim Summary

Parkinson's disease is a chronic progressive neurological disorder that affects approximately 100/100 000 individuals. Onset generally occurs after 50 years of age and its incidence increases as the population grows older. While PD has historically been considered as a motor disorder with hallmark features that include resting tremor, rigidity, bradykinesia and postural instability, it is now accepted that the disorder also includes a decline in behavioural and cognitive functioning that begins with subtle impairments, and for many results in dementia. Moreover, it is becoming evident that the cognitive and behavioural symptoms associated with PD may be as

debilitating as the motor symptoms, and are associated with reduced quality of life and caregiver distress.

Loss of dopamine-containing neurons in the substantia nigra and its projections to the basal ganglia is considered the focus of neuropathology in PD. Contemporary models of how the basal ganglia function suggest that the basal ganglia are involved in at least 5 parallel loops with the cerebral cortex, two of which are involved in motor functioning, with the remaining three implicated in cognition and behaviour. Deficits associated with PD are thought to result from dysfunction in these loops, secondary to the depletion of dopamine-containing neurons in the substantia nigra that project to the basal ganglia.

Consistent with the dopamine theory, many of the motor symptoms associated with PD are substantially ameliorated with dopamine replacement. However, a more complex pattern of improvement has been reported for cognitive and behavioural deficits. A number of explanations have been offered for this, including the "over dose hypothesis" which suggests that the levels of dopamine that are required to ameliorate the motor complications of PD "over dose" more intact structures that are implicated in cognitive and behavioural functions. Alternatively, the other structures and systems that have been shown to degenerate in PD may contribute to the cognitive and behavioural dysfunction associated with this disorder. For example, in addition to the main closed circuits suggested by Alexander et al. (1986), the frontal lobes are reciprocally connected to functionally similar areas of the brain via a number of open afferent and efferent connections that also deteriorate as part of the PD process. Moreover, there has been evidence of abnormalities in other subcortical structures, evident from the early stages of the disease process. This diverse pattern

of degeneration is thought to underlie the heterogeneous cognitive and behavioural features of PD.

While there has been considerable interest in identifying the cognitive and behavioural features associated with PD, there has been inconsistency in the literature regarding what functions are impaired. Much of this inconsistency has resulted from the application of different methodologies and diverse patient group characteristics. Despite the limitations in the literature, a general pattern of cognitive domains that are more likely to be impaired in people with PD has been identified including: visuoperception/visuospatial, speed of mental processing, memory and learning, and executive functions (including, planning, working memory, attention, verbal function and decision making). Much of the more recent research regarding cognitive deficits in PD has focused on deficits in executive functions. These facets of cognition are of particular importance because it is likely that they will impact on other areas of cognitive ability. A number of neuropsychiatric symptoms have also been reported in PD, the most common of these being depression, anxiety, apathy, and fatigue, which are reported in up to 80% of people suffering from this disorder.

1.13 Direction of Current Research

As is evident in this review, cognitive and behavioural disorders associated with PD have generated considerable research interest with disparate results. However, one consistent finding is that people with PD represent a heterogeneous group with a variety of cognitive, behavioural, and motor symptoms. In an effort to identify which people with PD will have cognitive difficulties, researchers have examined outcomes using a number of different groupings ie., frontal versus non-frontal symptoms (Berry, Nicolson, Foster, Behrmann, & Sagar, 1999), sporadic

versus familial PD (Dujardin, Defebvre, Grunberg, Becquet, & Destee, 2001), motor symptoms (Dujardin, Defebvre, Grunberg, Becquet, & Destee, 2001; Lewis et al., 2005), executive dysfunction (Lewis et al., 2003), and age at onset (Katzen, Levin, & Llabre, 1998). A relatively common classification system has been motor symptomology, which is intuitively appealing given the neuropathology of PD. However, motor symptoms do not consistently correlate with cognitive or behavioural symptoms (Graham & Sagar, 1999). As Graham and Sagar (1999) point out, classification systems have frequently been based on intuition, with little consensus regarding how different factors interact to disrupt cognitive and behavioural functions.

This current research aims to use a data-driven method of identifying different sub-categories of people with PD, using the general concept of Mild Cognitive Impairment. Mild cognitive impairment (MCI) is a term used in the dementia literature to describe cognitive impairments that exceed the level of impairment usually evident with normal aging, but not sufficiently severe to warrant a diagnosis of dementia (Petersen, 2000; Petersen, 2004; Petersen et al., 2001). There has been some debate regarding how MCI should be defined, but more recently it has been recognised that multiple clinical subtypes exist: MCI amnestic type (typical of AD), MCI with cognitive deficits in multiple cognitive domains (language, executive function, visuospatial skills) with or without memory deficits, and MCI single cognitive domain with no memory impairment (Petersen, 2004). The second subtype is considered more characteristic of people with PD and MCI (PD-MCI).

The concept of MCI has only recently been formally investigated in relation to PD (Caviness et al., 2007; Woods & Troster, 2003) and it has been suggested that the

cognitive impairments in people with PD form a continuum from mild and subtle, to severe and overt (Stern et al., 1998). Therefore, PDD could be viewed as the most severe end of the spectrum in terms of cognitive impairments, with PD-MCI forming a clinical entity that may represent those with preclinical PDD. This line of research may provide an important avenue for understanding cognitive deficits in PD.

The concept of PD-MCI presents an opportunity to intervene and delay the onset of more severe cognitive problems that may result in later dementia. Techniques such as functional imaging and eye movements have been proposed as useful in identifying early markers of PDD. However, these methods are costly and not widely available, whereas a brief cognitive assessment provides a less invasive and cost effective method of identification that can be administered by a range of health professionals. Moreover, research indicates that, as with AD, the impairments associated with PDD may be improved with cholinesterase inhibitors without worsening motor symptoms (see Burn & McKeith, 2003 for review). Therefore, early identification of individuals likely to develop PDD could be the basis for intervention that could slow its development. This is extremely important given the reduced quality of life associated with dementia, increased caregiver distress, and the resultant premature rest home placement.

1.14 Objectives of the Current Research

The general aim of this thesis is to contribute to the understanding of cognitive and behavioural deficits pertinent to everyday functioning in people with PD by specifying some of the relationships between these measures. A central theme of this research is to explore whether sub-groups of people with PD can be identified based on their cognitive profile, specifically, to identify people with PD who could be

considered as suffering from MCI. This is important as currently there is no agreed single set of tests that can be used to identify patients with PD who might be experiencing cognitive impairments that are not severe enough to warrant a diagnosis of dementia, but are of clinical relevance in that they affect aspects of everyday functioning. Furthermore, identification of these subgroups may enhance our understanding of cognitive impairments in PD. Moreover, timely identification of individuals with clinically significant levels of impairment is essential as it provides an opportunity to introduce appropriate treatment strategies, reduce personal and caregiver distress, and thus avoid premature rest home placement. In line with this central theme, this thesis has a number of objectives:

1.14.1 Objective 1: Develop a Cognitive and Behavioural Profile

An initial objective of the project is to identify some of the pertinent cognitive, behavioural, and psychiatric deficits in PD patients compared with the normal elderly. This overlap is of particular importance as PD is primarily a disorder of the elderly, therefore observed deficits must be contrasted with the cognitive and behavioural effects of normal aging (Bennett et al., 2002; Dubois, Pillon, Sternic, Lhermitte, & Agid, 1990). Given the association between PD and the frontal-striatal circuits, it is expected that executive functions are particularly vulnerable in individuals with PD. There is extensive literature regarding cognitive and behavioural outcomes and PD, however, the exact nature and extent of these deficits remains a matter of debate (Kulisevsky et al., 1996). This objective will enable us to more fully define the extent of these deficits in PD compared with normal aging.

1.14.2 Objective 2: Determine Functional Deficits Associated with Parkinson's Disease

As characteristic motor dysfunctions are often the focus of treatment intervention for PD, the more subtle deficits that result in an individual's inability to function efficiently in their environment may be overlooked. Therefore, the second objective will be the identification of functional deficits that may be associated with PD, using measures of cognitive, behavioural and psychiatric deficits and everyday living tasks.

1.14.3 Objective 3: Identification of Sub groupings

The central focus of this thesis is to explore whether subgroups of patients can be identified based on their cognitive profile. Identification of these different sub categories of people with PD will use the general concept of Mild Cognitive Impairment to develop a unique method of classifying cognitive impairments for people with PD but without dementia (PD-MCI). It is intended that a brief battery of tests (using information gained from objective 1 and 2) will be identified to distinguish different groups using a data-driven exploratory method involving cluster analysis.

1.14.4 Objective 4: Confirmation of Groupings

A follow-up study will examine the stability of cognitive groupings that emerge from the initial main study. Individuals who are involved in the initial study will be invited to participate in a follow up study that will use the tests identified in phase one of this research to examine if they are indeed useful in terms of determining

sub-categories. It would be expected that individuals would either remain in their original groupings, or show a decline in functioning.

It is intended that a discrete group of non-invasive tests may be identified that will have clinical application. A related goal of this objective will be to define which tests, from a number of conceptually related tests, are most sensitive or appropriate for use with PD patients.

1.14.5 Objective 5: Complex Language and Parkinson's Disease

Deficits in complex language have been associated with PD, with speed of processing and working memory being suggested as mediating any deficits. However, there is considerable debate as to the exact nature of the relationship between complex language and these variables. Therefore, as the fifth objective, the identification of the relative contribution of working memory and speed of processing on complex language skills, will be undertaken. In addition, this project will look at the association between complex language skills and social functioning.

Chapter 2 – Method

Abbreviations used in the text Chapter Two

1) **AD** = Alzheimer's disease; 2) **BADS** = Behavioral Assessment of the Dysexecutive Syndrome; 3) **BADLS** = Bristol Activities of Daily Living Scale; 4) **BDI-II** = Beck Depression Inventory; 5) **CANTAB** = Cambridge Neuropsychological Test Automated Battery; 6) **CPT** = Continuous Performance Task; 7) **DEX** = The Dysexecutive Questionnaire; 8) **D-KEFS** = Delis Kaplan Executive Function System; 9) **DOT-A =** The Adaptive Digit Ordering Task; 10) **DRS-II** = Dementia Rating Scale-II; 11) **DSM-IV** = Diagnostic and Statistical Manual Fourth Edition; 12) **ED** = Extra Dimensional shift; 13) **EXIT** = The Executive Interview; 14) **FAQ** = Functional Activities Questionnaire; 15) **FrSBE** = Frontal Systems Behaviour Scale; 16) **GDS** = Geriatric Depression Scale; 17) **HADS** = Hospital Anxiety Depression Scale; 18) **H&Y =** Hoehn and Yahr Staging Scale; 19) **ID/ED** = Inter Dimensional/Extra Dimensional Shift; 20) **IQCODE** = The Informant Questionnaire on Cognitive Decline in the Elderly; 21) **JOL** = Judgement of Line Orientation test; 22) **MMSE =** Mini Mental Status Exam; 23) **3MS** = Modified Mini Mental Status Exam; 24) **NART** = National Adult Reading test; 25) **NPI** = Neuropsychiatric Inventory; 26); **PD** = Parkinson's disease; 27) **PDD** = Parkinson's disease with dementia; 28) **PDQ-39 =** The Parkinson's Disease Questionnaire; 29) **ROF** = Rey-Osterrieth Complex Figure Test; 30) **SN** = Substantia nigra; 31) **TEA** = Test of Everyday Attention; 32) **TOL** = Tower of London; 33) **TLC-E** = Test of Language Competence Expanded Edition- Level 2; 34) **UPDRS** = Unified Parkinson's disease Rating Scale; 35) **VAT** = Visual Association Test; 36) **VOSP =** The Visual Object and Space Perception Battery; 37) **WASI =** Wechsler Abbreviated Scale of Intelligence; 38) **WAIS-III** = Wechsler Adult Intelligence Scale 3rd edition; 39) **WMS-III** = Wechsler Memory Scale-3rd Edition.

2.1 Justification of Tests Selected

In keeping with the main objective of this study, namely the development of a cognitive and behavioural profile of people with PD without dementia, a wide range of tests were administered over five testing sessions (three of these were conducted for study one and two during the follow-up study). The selection of tests was determinded by theoretical and empirical findings, and subject characteristics (see Table 9 for outline of tests selected).

2.1.1. Theoretical Basis

The major theory in PD research is the dopamine theory. To briefly recap, this theory proposes that Parkinson's disease is associated with a decrease in dopamine in the basal ganglia secondary to degeneration of dopamine neurons in the substantia nigra. A major consequence of the depletion of dopaminergic neurons is a disruption of the basal ganglia-thalamocortical circuits which are implicated in both motor and non-motor functions. Of specific relevance to this study are the dorsolateral, orbitofrontal and anterior cingulate circuits, outlined by (Alexander, DeLong, & Strick, 1986), which have been associated with a range of behavioural and cognitive disorders. Disorders associated with each of the circuits are briefly outlined below. Each circuit is proposed as having a pre-eminent, if not exclusive, role in the performance of different functions.

A) Dorsolateral prefrontal circuit: The integrity of this circuit is associated with the effective performance of executive functions, the ability to integrate cognitive and perceptual processes across time and space and update goals in the face of new information. Executive functions include working memory, decision

making, flexibility, set maintenance, self monitoring and control of ongoing behaviour (Roberts & Pennington, 1996; Salthouse, 2005; Samango-Sprouse, 1999).

B) The Orbitofrontal circuit mediates socially appropriate behaviours. Personality changes are most commonly seen after disruption of this circuit and may include irritability and changes in mood (Mah, Arnold, & Grafman, 2005). Patients with lesions in this area may behave inappropriately in social situations, often failing to respond to environmental and social cues (Chow & Cummings, 1999; Mah, Arnold, & Grafman, 2005).

C) The Anterior cingulate: This circuit is involved in motivated behaviour (Tekin & Cummings, 2002). Patients with lesions in the structures of the anterior cingulate are reported to be apathetic with impaired motivation along with poor response inhibition and may show a reduction in creative thought (Chow & Cummings, 1999).

Measures selected for use in this study focused on assessing deficits considered likely with dysfunction of the dorsolateral, orbito-frontal and anterior cingulate circuits, to provide a theoretically relevant range of measures.

2.1.2 Empirical Basis

A general pattern of cognitive domains that are more likely to be impaired in patients with PD has emerged from the extensive literature in this area, as has been reviewed in section one. These include deficits in verbal function, visuoperception, visuospatial skills, speed of mental processing, memory, learning and executive functions (including, planning, working memory and attention). Moreover, impairments in executive functioning and working memory have consistently been

reported, even from the early stages of the disease process (Bondi, Kaszniak, Bayles, & Vance, 1993b; Levin & Katzen, 1995). Therefore, we selected tests that had been demonstrated in the literature to detect deficits in PD, with a particular focus on executive functions and working memory.

A number of screening tests for dementia were included in our battery. This was of particular importance as this study aims to identify different sub-categories of people with PD without dementia, with an emphasis on generating criteria for PD-MCI. Therefore, it was critical that the screening tests identified people who suffering from dementia in order to exclude them from this study.

There is no generally agreed on battery of tests that are used to assess cognitive and behavioural deficits associated with PD. Indeed different tests which theoretically assess the same function are used interchangeably by researchers and may lead to some of the disparate findings in the literature. Therefore some of the tests were selected to assess whether they were indeed interchangeable or whether some were more sensitive to problems associated PD than others. For example, three different measures of depression were selected, the Geriatric Depression Scale, the Beck Depression Scale-II and the Hamilton Anxiety and Depression Scale.

2.1.3 Subject Characteristics

Another major consideration in the selection of tests was the likely subject characteristics that may affect optimal performance. Specifically we wanted to ensure that deficits in performance were not due to the motor problems associated with PD. Individuals with motor symptoms ranging from mild to severe were included in in this research. Therefore, tests were selected that involved a minimal motor component. Where motor skills were required, tests with minimal speed component were used.

The literature also suggests that fatigue may be a major problem for some people with PD and sessions were expected to last approximately three hours (most lasted between 3-4 hours) depending on the individual. Therefore, tests that were of short duration (the majority took under 15 minutes to complete) were chosen so that frequent breaks could be provided as required (these tests are listed on Table 10 numbers indicate where each test may be found in list of test descriptions).

Table 10: Test selected to assess cognitive and behavioural functions in people with Parkinson's Disease versus healthy controls.

Initial Screening /Background tests
Beck Depression Inventory (BDI-II) [3]
Dementia Rating Scale-II (DRS-II) [10]
Ethnicity Data (see Appendix I for a copy)
General Health and demographic screen (see Appendix II for copy) [16]
Geriatric Depression Scale (GDS) [17]
Hospital Anxiety and Depression Scale (HADS)[18]
Mini Mental Status Exam (MMSE) [22]
Modified Hoehn and Yahr [23]
National Adult Reading Scale-II (NART-II) [25]
The Executive Interview (Exit) [33]
The Modified MMSE (3MS) [22]
Unified Parkinson's disease Rating Scale (UPDRS) [38]
Vocabulary- *Subtest from the Wechsler Abbreviated Scale of Intelligence* (WASI) [41]
Tests of Executive Function /Planning
Category Fluency -*Subtest from the Delis Kaplan Executive Function System* (D-KEFS) [9]
Category Fluency-switching (D-KEFS) [9]
CLOX- I [6]
Design Fluency-Filled dots (D-KEFS) [9]
Design Fluency-Switching (D-KEFS) [9]
Intra dimensional/ Extra dimensional Shift -*Subtest from the Cambridge Neuropsychological Test Automated Battery* (CANTAB) [5]
Key Search -*Subtest from Behavioural Assessment of the Dysexecutive Syndrome* (BADS) [4]
Letter Fluency (D-KEFS) [9]
Stroop (Switching- D-KEFS) [9]
Stockings of Cambridge (CANTAB) [5]
Theory of Mind Test [30]
Tower of Hanoi (D-KEFS) [9]
Zoo Map - (BADS) [4]

Table 10: Continued.

General Memory

- Auditory Recall - *Subtest from the Wechsler Memory Scale -3rd edition* (WMS-III) [42]
- Logical Memory I&II (WMS-III) [42]
- Paired Associates I&II (WMS-III) [42]
- Rey-Osterrieth Complex Figure Test II&III (ROF) [27]
- Visual Association Test (VAT) [39]

Problem Solving

- Matrix Reasoning (WASI) [41]
- Card Sort (Free) (D-KEFS) [9]
- Tower of London Revised (TOL-R) [37] (see Appendix III for instructions)
- Gambling Task [15](See Appendix IV for instructions)

Speed of Processing

- Digit symbol coding -Wechsler Adult Intelligence Scale 3rd edition (WAIS-III) [11]
- Motor copying (WAIS-III) [24]
- Stroop (word naming – D-KEFS) [9]
- Stroop (color naming- D-KEFS) [9]

Tests of Working Memory/Attention

- Continuous Performance Task (CPT) [7](See Appendix V for instructions)
- Daneman and Carpenter Reading Span Test [8] (See Appendix VI for list of words and instructions for Study One. Appendix VII shows words and instructions for Study Two)
- Digits Forward (WMS-III) [42]
- Digits Backward (WMS-III) [42]
- Letter Number Sequencing (WMS-III) [42]
- Spatial Span (CANTAB) [5]
- Spatial Working Memory (CANTAB) [5]
- Memory for Temporal Order (Word sequencing test) [20] (See Appendix VIII for list of words used)
- Memory for Temporal Order Revised [21](See Appendix IX for list of words used
- Map Search – *Subtest from Test of Everyday Attention* (TEA) [28]
- The Digit Ordering Task (DOT)[32]

Visuoperceptual/Visuoconstruction

- CLOX-II [6]
- Incomplete letters- *Subtest from The Visual Object and Space Perception Battery* (VOSP) [40]
- Judgement of Line Orientation [19]
- Object Decision Task (VOSP) [40]
- ROF-I [27]

Language

- Test of Language Competence Expanded Edition-Level 2 (TLC-E) [29]

NOTE: Numbers indicate where the description of the test may be found in the list at the end of the method section.

Another unique feature of this study was to examine the relationship between cognitive and behavioural deficits and aspects of everyday living. As patients sometimes underestimate or minimise the extent of any deficits due to lack of insight

or problems with memory, tests were also selected for use with a person who knew the participant well (see Table 11).

Table 11: Tests selected to assess Activities of Daily Living in People with Parkinson's Disease versus Controls.

Activities of Daily Living *(completed by significant other)*
Bristol Activities of Daily Living Scale (BADLS) [2]
Frontal Systems Behaviour Scale (FrSBe) [13]
Functional Activities Questionnaire [14]
Neuropsychiatric Inventory (PD patients only) [26]
The Clinical Assessment of Fluctuation [31](PD patients only)
The Dysexecutive Questionnaire (DEX) [3]
The Informant Questionnaire on Cognitive Decline in the elderly (IQCODE)[34]
The One Day Fluctuation Assessment Scale [35] (PD patients only)
Activities of Daily Living *(completed by participant)*
Apathy Scale [1]
DEX (self report) [4]
Fatigue Severity Scale [12] (See Appendix X for instructions)
FrSBe (self report) [13]
Parkinson's Symptom and Sleep Diary (PD Patients only) (See Appendix XI)
The Parkinson's Disease Questionnaire (PDQ-39) [36] (PD patients only)

2.2 Study One - Thinking and Language Skills in Parkinson's Disease

2.2.1 Participants

Parkinson's disease group

Parkinson's patients in the Canterbury region, who had not been diagnosed with dementia, were invited by letter to participate in the study by two consulting neurologists employed by Christchurch Hospital. Included with the letter of invitation were an information sheet and a reply slip. The reply slip was to be returned if the

patient consented to volunteer for the study (see Appendix XII, XIII, and XIV for copies of letter, information sheet and reply slip respectively). The study received approval from the Canterbury Ethic Committee (see Appendix XV for a copy of ethics approval).

Participants were required to meet the following inclusion/exclusion criteria:

Inclusion Criteria:

- A diagnosis of idiopathic Parkinson's disease, confirmed by a neurologist using the UK Parkinson's Disease Society Brain Bank Clinical Diagnostic Criteria (see Section One, Table 2).
- Assessed at the Hoehn & Yahr stage 1-IV.
- Aged between 50 and 80 years old.
- Sufficient motor control to participate in testing, with no uncontrolled dyskinesia.
- Adequate or corrected hearing and vision (self report checked by examiner).

Exclusion Criteria:

- Involved in current therapeutic trial.
- History of:
    - Moderate or severe head injury.
    - Stroke or other neurological impairment.
    - Major medical illness (e.g. severe cardiovascular problems, type II diabetes).

    - Significant psychiatric illness requiring hospitalisation.

- Overt dementia (MMSE <25).
- Hallucinations.
- Alcohol or substance abuse.
- Diagnosis of, or special education for, a learning disability.
- Major depression in the previous 6 months.
- Pre-morbid IQ estimated at <85 using National Adult Reading Test (NART).
- Currently taking medications known to have a significant effect on Central Nervous system (other than medications prescribed for the control of PD symptoms).
- Beck Depression Inventory –II score of >17.

Of the total 115 letters that were posted out, 6/115 (5.2%) of individuals with PD were too unwell to participate, 6/115 (5.2%) were deceased, 8/115 (6.9%) declined, and 34/115 (29.6%) did not respond. In total, 61/115 (53%) individuals with PD completed at least one of the testing sessions. For the initial manuscripts that covered frequency of psychiatric problems, and sensitivity of depression measures, (see section 3) the inclusion criterion was a diagnosis of PD and the exclusion criterion was evidence of dementia. For this aspect of the study, 59 patients were used. Two of the 61 patients had to be excluded as they had evidence of dementia. No controls were required for these analyses.

However, for all other analyses and manuscripts, it was essential to have stringent inclusion/exclusion criteria so that accurate conclusions could be drawn regarding the impact on cognition for patients with PD, without dementia, compared to healthy older people. For the main study, twenty one of the 61 PD participants did not meet the inclusion/exclusion criteria listed above, leaving 40 participants with PD who were available for inclusion in the main study (the main study is covered in Sections 4,5, and 6, and examines aspects of cognition and language for PD patients versus healthy older people).

Controls

Controls were recruited from a number of sources including a previously established data base, and by advertisements at local clubs (bowling, tramping and table tennis clubs) and businesses (see Appendix XVI for a copy of the advertisement). Controls that were part of the established data base were initially contacted by phone. All controls were given a brief outline of the study on first phone contact. If they were willing to participate they were then sent an information sheet (see Appendix XVII for copy of the information sheet).

In addition to adequate or corrected hearing and vision (self report, checked by the examiner) and being aged between 50 to 80 years of age, the same exclusion criteria listed above also applied to the control group. A total of 65 controls completed at least one of the testing sessions. Group and demographic characteristics are shown in Table 12 and Table 13 respectively. Each of the 40 PD patients included in the main study were matched as closely as possible to healthy controls in terms of age (± 5 years of the matched control age, mean = 2.91 years) and pre-morbid IQ using the NART (± 5 points of the matched control score, mean = 2.29 points). Such

a close match was not possible in 7/40 cases for age and 6/40 cases for ratings of pre-morbid IQ. In these cases, matching was within ± 5-9 years for age and ± 5-8 points for NART scores. Matching was confirmed by t-statistics (IQ: $t = 0.94$, $df = 78$, $p > 0.30$; and age: $t = 0.31$ df = 78, $p > 0.75$). There were significantly more males in the PD group (PD 26 /40 [65%] v Control 13/40 [32.5%]) ($\chi^2(df, 1) = 8.46$, $p = <0.01$).

Table 12: Group characteristics of Parkinson's disease patients versus controls.

	Parkinson's disease (n=40)			**Control Group (n=40)**				
	Mean	**SD**	**Range**	**Mean**	**SD**	**Range**	***t*-vlaue**	***p*-level**
NART[1]	109.05	[10.13]	87-131	111.20	[10.30]	90-128	0.94	>0.30
Education[2]	13.94	[2.56]	11-22	13.76	[2.57]	8-20	0.30	>0.75
Age	66.15	[6.65]	52-77	66.58	[5.47]	52-76	0.31	>0.75
MMSE[3]	28.65	[1.42]	25-30	29.58	[0.71]	28-30	3.67	<0.001*
BDI-II[4]	7.59	[4.34]	0-16	4.13	[3.39]	0-15	-3.96	<0.001*

[1]National Adult Reading Test, [2]Total number of years formal education, [3]Mini Mental Status Exam, [4]Beck Depression Inventory, * significant at $p<0.05$

Table 13: Group characterstics for Parkinson's disease patients.

	Mean	**SD**	**Range**			
PD onset[1]	6.49	[4.35]	0.25-23			
UPDRS[2]	28.46	[9.49]	13-49			
H&Y[3]	Level 1	Level 1.5	Level 2	Level 2.5	Level 3	Level 4
	(n=8)	(n=6)	(n=7)	(n=10)	(n=7)	(n=2)

[1]Number of years since onset of Parkinson's disease symptoms, [2]Unified Parkinson's disease Rating Scale (motor score component), [3]Hohen & Yahr stage

2.2.2 Procedure

All participants were asked to attend three testing sessions, each lasting an average of three hours. Testing sessions were scheduled one week apart. However, due to other commitments of the participants on some occasions this was not possible and in these cases sessions were scheduled at slightly longer or shorter intervals.

Session 1:

At the beginning of the first visit, the study objectives were explained to the participant and consent forms were signed (See Appendix XVIII). During this session general background information was collected, this included demographic details, educational history, alcohol and drug use, medications that were being taken and ethnicity data. Information regarding current mental status and general past and present cognitive functioning was also collected. For PD patients only, information regarding severity of illness was assessed (using the unified Parkinson's disease Rating Scale, The Modified Schwab and England Activities of Daily Living Scale and the Modified Hoehn and Yahr scale).

During this session participants completed self report questionnaires regarding their mood. If any participant scored ≥ 14 BDI-II or ≥ 9 on the GDS they were given an information sheet regarding the implications of low mood. They were also asked to consent to the researcher contacting their general practitioner so that the participant could be provided with further advice (see Appendix XIX and XX for these information sheets). If any participant indicated that they had suicidal ideation or if they scored ≥ 19 on the BDI-II or ≥ 15 on the GDS then, as a further safety measure a full depression screen was conducted by a registered clinical psychologist.

At the end of the first session, participants were asked to take home a selection of standard self-report questionnaires to fill in and return at the next visit. Also, if the participant consented, collateral information regarding the participants daily functioning was collected from an individual, volunteered by the participant, who knew the participant well (See Appendix XXI for consent form). For individuals with PD, interviews with the significant other person were conducted by a trained research assistant and took place in an adjoining room while the participant was engaged in the second or third testing session. For individuals acting as controls, information for significant others to complete was sent home with the participant and bought back at the next session. See Table 14 for order of test presentation, and Table 15 for a list of tests conducted with significant others and tests completed by participants at home.

Sessions 2 & 3:

Sessions two and three included more specific memory, language and planning measures. At the end of session two, participants were again asked to take home a selection of standard self report questionnaires to fill in and return at the next session. At the end of session three participants were asked if they would consent to being contacted for a follow up study. See Table 14 for the order of test presentation for sessions two and three.

To minimise fatigue, testing in each session was arranged to enable unscheduled breaks to be taken as required. To enable this flexibility, tests were also selected with brevity in mind and were a maximum of 20 minutes in duration, with the majority taking between 10-15 minutes to complete. There was also one compulsory 20 minute break in each session during which the participants were provided either a morning or afternoon tea. All participants were reimbursed $20

towards transport costs for each visit, or if required, the cost of a taxi within the Christchurch region. Approximately six months following the completion of the main study, a brief outline of information regarding the outcomes were sent to participants (see Appendix XXII for copy).

Table 14: Order of test presentation for each of the three testing sessions.

Session One	Session Two	Session Three
Signing of consent forms	Logical Memory 1 (WMS-III).	Theory of mind test
Health questionnaire	Paired Associates I (WMS-III)	L.N Sequencing test (WMS-III subtest)
Mini Mental Status Exam (MMSE/3MS)	The Daneman and Carpenter Reading Span Test	Digit Span (WMS-III subtest)
Geriatric Depression Scale	Key Search (BADS subtest)	Zoo Map (BADS subtest)
ROF (copy phase)	Logical Memory II (WMS-III subtest)	Card Sort (D-KEFS subtest)
2.5 minute break	Paired Associates II (WMS-III subtest)	Motor screen (CANTAB subtest)
ROF 1st recall phase (after 3 minute delay)	Digit symbol coding (WAIS-III subtest)	Spatial Working Memory (CANTAB subtest)
Vocabulary (WASI subtest).	Motor copying (WAIS-III. subtest)	ID/ED shift (CANTAB subtest)
EXIT (Part one)	Ambiguous Sentences (TLC-E subtest)	
ROF 2nd recall phase (after 30minute delay)	Listening Comprehension (TLC-E subtest)	
BREAK	**BREAK**	**BREAK**
Memory for Temporal order	Motor Screen (CANTAB subtest)	Verbal Fluency (D-KEFS subtest)
VAT	Stockings of Cambridge (CANTAB subtest)	Design Fluency (D-KEFS subtest)
DRS-2	Spatial Span (CANTAB subtest)	Tower (D-KEFS subtest)
NART	Oral Expression (TLC-E subtest)	Stroop (D-KEFS subtest)
Matrix Reasoning (WASI subtest)	Figurative Language (TLC-E subtest)	Judgement of Line Orientation
EXIT (Part two)	Frontal Systems Behavioural Scale	
CLOX I&II	Homework explained	
BDI		
Homework Explained		
PD patients only:		
UPDRS		
Modified Hohen &Yarh		
Schwab and England Activities of Daily Living Scale		

Table 15: Tests completed by significant others and additional questionnaires completed by participants at home.

Completed by significant other	
	Functional Activities Questionnaire
	The Dysexecutive Questionnaire (DEX)
	Frontal Systems Behaviour Scale (FrSBe)
	Neuropsychiatric Inventory (PD patients only)
	The Clinician Assessment of Fluctuation and the One Day Fluctuation Assessment Scale (PD patients only)
Completed by participant for homework	
	DEX (self report)
	HADS
	Apathy Scale
	Fatigue Questionnaire Scale
	The Parkinson's Disease Questionnaire (PDQ-39) (PD patients only)

2.3 Study Two - Developing Cognitive Measures for Parkinson's Disease

2.3.1 Participants

Participants were approached for retesting on average one year following the main study (The minimum period of follow up was 9 months and the maximum of 16 months). Participants who had given consent (39/40 people with PD and 40/40 of the healthy controls had consented at the end of first phase of testing) were first contacted by phone to ascertain whether they were still willing to participate in the second study, and if willing, given details of the studies objectives. Participants were then sent an information sheet (see Appendix XXIII for copies of the information sheet used for both PD patients and controls). The study received approval from the Canterbury Ethic Committee (see Appendix XXIV for copy of ethics approval).

Of the 39 patients who consented to being re-contacted, 33 were available for testing at follow-up. Of the six subjects that were unavailable; one was deceased; two had been hospitalised; one was out of the city during the testing period; one declined; and one was unable to be contacted. Controls that were matches for the patients with PD were also contacted. Of the people with PD that were not available for follow-up 2 came from group 1, 1 came from group 2 and 4 came from group 3. Parkinson's patients who did not participate at time two tended to be older (mean 72.1 v 64.9, t=-2.86, df=38, p<0.01) and had lower scores on the MMSE (mean 27.4 v 28.9, t=2.69, df=38, p<0.02).

Demographic characteristics of the available participants and their matches are shown on Table 16 and 17. Patients and controls were required to meet the original inclusion/exclusion criteria outlined in the main study with the exception that individuals with low mood were included in the analyses. There were significantly more males in the PD group (PD 23 /32 [72.0%] v Control 10/32 [31.3%]) (χ^2 (df,1) = 10.57, p <0.01).

Table 16: Group characteristics, Parkinson's disease patients versus controls.

	Parkinson's disease (n=32)			**Control Group (n=32)**				
	Mean	[SD]	Range	Mean	[SD]	Range	*t*-value	*p*-level
NART[1]	109.13	[10.63]	87-131	111.00	[10.79]	90-127	0.70	>0.45
Education (yrs)[2]	13.90	[2.88]	11-22	13.76	[2.57]	8-20	-0.31	>0.75
Age	64.90	[6.66]	52-77	65.38	[5.09]	52-76	0.31	>0.75
MMSE[3]	28.84	[1.2]	26-30	29.68	[0.59]	28-30	-3.46	**<0.001***
BDI-II[4]	9.06	[4.29]	0-21	4.47	[5.05]	0-24	-3.92	**<0.001***

[1]National Adult Reading Test, [2]Total number of years formal education, [3]Mini Mental Status Exam,[4]Beck Depression Inventory.

Table 17: Group characteristics for Parkinson's disease patients.

	Mean	SD	Range			
PD onset[1]	6.38	[4.61]	0.25-23			
UPDRS[2]	27.84	[8.00]	14-46			
H&Y[3]	Level 1 (n=3)	Level 1.5 (n=6)	Level 2 (n=6)	Level 2.5 (n=6)	Level 3 (n=10)	Level 4 (n=1)

[1]Number of years since onset of Parkinson's disease symptoms, [2]Unified Parkinson's disease Rating Scale (motor score component), [3]Hohen & Yahr stage

2.3.2 Procedure

Each participant was required to attend two testing sessions, each lasting an average of three hours. Testing sessions were scheduled one week apart. However, occasionally, due to other commitments of the participants it was not possible to organise sessions in this way and in these cases sessions were scheduled at slightly longer or shorter intervals (see Table 17 for the order of test presentation for sessions one and two).

Session 1:

At the beginning of the first visit, the study objectives were explained to the participant and consent forms were signed (See Appendix XXV, the same consent form was used for both PD patients and controls). During this session general background information was collected including, alcohol and drug use and medications that were being taken, and information regarding medical history for the intervening period of time between the two study phases. Also, additional information regarding hallucinations was collected (See Appendix XXVI for health check list used for both PD patients and Control participants and hallucination screening questions).

Information regarding current mental status was collected for all patients and for PD patients only; information regarding severity of illness was reassessed (using the Unified Parkinson's disease Rating Scale, The Modified Schwab and England Activities of Daily Living Scale and the Modified Hoehn and Yahr scale).

At the end of the first session, participants were asked to take home a selection of standard self-report questionnaires to fill in and return at the next visit. Also, if the participant consented (See Appendix XXVII for consent form used for both PD and Control participants), collateral information regarding daily functioning was collected from an individual, who knew the participant well. For individuals with PD, interviews with the significant other person were conducted by a trained research assistant and took place in an adjoining room while the participant was engaged in the second testing session. For individuals acting as controls, information for significant others to complete was sent home with the participant and bought back at the next session. See Table 18 for order of test presentation and Table 19 for a list of tests conducted with significant others and tests completed by participants at home.

Session 2

The tests used in session two were selected from the tests shown in the main study to identify the different groupings of PD patients and included measures of general memory and cognition and executive functioning. Specific measures of decision making and planning were also included in this session. At the end of session two, participants were asked if they would consent to being contacted by the principle researcher (A.M) for a follow up study (it was intended to follow the patients over time to determine the cognitive and psychiatric problems that were predicative of decline into dementia).

To minimise fatigue, testing in each session was arranged to enable unscheduled breaks to be taken as required. To enable this flexibility, tests were also selected with brevity in mind, and were a maximum of 15 minutes in duration, with the majority taking less than 10 minutes to complete. There was also one compulsory 15 minute break in each session during which the participants were provided either a morning or afternoon tea. All participants were reimbursed $20 for each visit towards transport costs, or if required, the cost of a taxi within the Christchurch region.

Table 18: Order of test presentation for each of the two testing sessions.

Session One	Session Two
Signing of consent forms	Digit span (WMS-III)
General Health questionnaire	* The Adaptive Digit ordering test
Mini Mental Status Exam	Daneman & Carpenter
* Fragmented letters –Visual Object Space and Perception Battery (VOSP)	* Memory for Temporal Word Ordering Test Revised
* Object decision (VOSP)	
Matrix reasoning (WASI subtest)	Letter Fluency Test (D-KEFS)
FrSBe	Category Fluency Test (D-KEFS)
Tower of London Revised (TOL-R)	
BREAK	**BREAK**
CLOX 1 & II	Paired Associates-I (WMS-III)
* Continuous performance test	ROF-1 (copy only)
* Gambling Task	Distraction task 2.5 mins
DRS-2	ROF-2
BDI-II	* Planning task
Patients with PD only	Line Orientation Test
UPDRS	* Map Search (Test of everyday attention)
Modified Hohen & Yarh	Paired Associates-II (WMS-III)
Schwab and England Activities of Daily Living Scale	

*Tests that were unique to phase two of the study.

Table 19: Tests completed by significant others and additional questionnaires completed by participants at home.

Completed by significant other
Functional Activities Questionnaire
Frontal Systems Behaviour Scale (FrSBe)
Neuropsychiatric Inventory (PD patients only)
The Clinician Assessment of Fluctuation and the One Day Fluctuation Assessment Scale (PD patients only)
Bristol Activities of Daily Living Scale (BADLS)
Short IQCODE
Completed by participant for homework
Sleep Diary
The Parkinson's Disease Questionnaire (PDQ-39) (PD patients only)

2.3.3 Test Description

Following is a brief description of tests that were used in the various testing sessions, significant other interviews and homework. Tests are listed below in alphabetical order:

1. ***Apathy scale*** (Starkstein et al., 1992): The Apathy scale is a 14 item self-report measure. Participants were asked to indicate the extent to which each of 14 statements would apply to them, over the last month, using a 4 point scale (not at all=0, slightly=1, some=2, a lot=3). Low scores were indicative of higher levels of apathy.
2. ***Bristol Activities of Daily Living Scale: (BADLS)*** (Bucks, Ashworth, Wilcock, & Siegfried, 1996): Completed by a care giver, the BADLS is designed to assess the everyday ability of people who have memory difficulties. The caregiver was required to assess the "significant other" on their ability in 20 different areas of daily living including food preparation, dressing ability or ability to perform tasks

of daily hygiene. Each activity is rated 1-3 with higher scores indicating greater impairment. If the caregiver had difficulty with any of the questions they were asked to rate the person using the level of ability which was most indicative of their average performance over the previous 2 weeks. The scale also has a "not applicable" option, rated as 0. For the purposes of this study an additional option was added of "due to Parkinson's symptoms", also rated as 0.

3. ***Beck Depression Inventory-Second Edition*** **(BDI-II)** (Beck, Steer, & Brown, 1996): The BDI-II is a brief 21 item self report questionnaire that assesses an individual's mood over the previous two week period. Each item was rated on a 4 point scale from 0-3. Higher scores indicated the presence of a greater number of depressive symptoms. Suggested cut offs are 0-13 for normal/minimal depressive symptoms, 14-19 mild, 20-28 moderate and 29-69 severe depression (Beck, Steer, & Brown, 1996). A cut score of 16/17 has been suggested as most appropriate for identifying individuals with PD who have depression (Leentjens, Verhey, Luijckx, & Troost, 2000), and a score of >16 was adopted in this study as part of the exclusion criteria.

4. ***Behavioural Assessment of the Dysexecutive Syndrome (BADS):*** Two subtests from this battery were used, the Zoo Map and Key Search. Specific details regarding scoring are provided in the test manual (Wilson, Alderman, Burgess, Emslie, & Evan, 1996). A self report questionnaire was also used from this test battery.

   - ***Zoo Map*****:** This subtest is made up of two tasks. In task A, the "high demand trial", participants were presented with an A4 piece of paper on which there was a map of a zoo. Twelve different locations were shown on the map, with the participants being required to visit six designated locations. However, the task had a number of rules that the participant had to consider when planning their

route. Participants were required to plan and then show how they would visit each of designated places without breaking any of the rules. Instructions were provided verbally by the examiner, with a visual reminder of the locations that were required to be visited and the rules for the task, available at the top of the page above the map. In task B, the "low demand trial", participants were presented with a map of the zoo identical to, and using the same rules, as task A. However, in task B participants were not required to plan their route around the zoo; they were only required to follow the instructions provided verbally and visually at the top of the page. Points were deducted for rule violations, incorrect sequences for visiting the designated locations and time spent planning. Scores for each version range from 0-16, with higher scores indicating better performance. Scores for task A and B were combined and converted to a profile score that ranged from 0-4, with higher scores indicating better performance.

- ***Key Search Test:*** Participants were presented with an A4 piece of paper on which there was a 10cm square and a black dot 5 cm below the square. Participants were told to imagine that the square was a field in which they had lost their keys. Starting at the black dot, they were to draw a line to show how they would search the field to make absolutely certain that they would find their keys. The test was scored according to different components of the task and included: where the participant entered the field, where the participant finished the search, whether the line was continuous or broken and the type of search pattern (templates of possible search patterns are provided in the manual). Raw scores range from 0-16, with higher scores indicating better performance. Raw

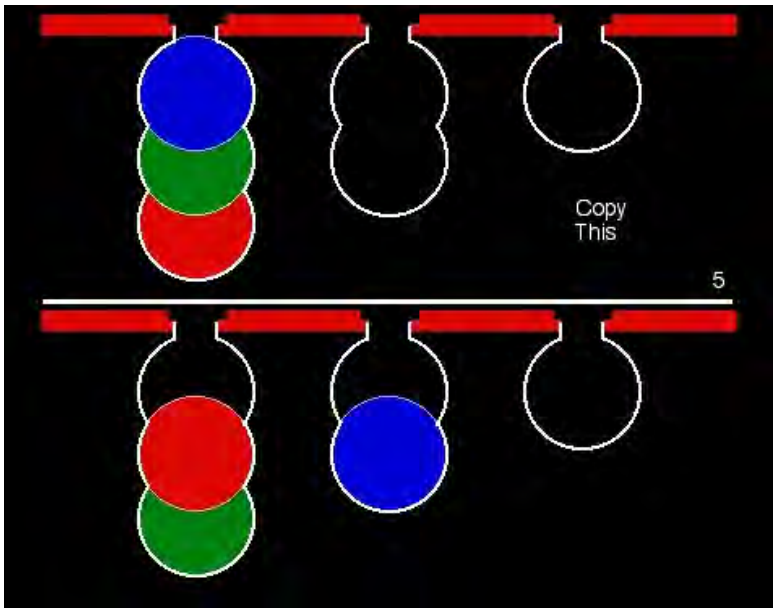
scores were converted to a profile score that ranges from 0-4 with higher scores indicating better performance.

- ***Dysexecutive Questionnaire (DEX):*** The DEX is a 20 item self report questionnaire that assesses symptoms associated with executive impairment. Questionnaire items cover three domains of functioning: behaviour, cognition, and emotion. There are two forms of the DEX. The first was completed by the participant and a second form was completed by a person who knew the participant well. The DEX contains 20 items rated on a 5 point scale (0 = never and 5 = very often) with higher scores indicating greater impairment.

5. ***Cambridge Neuropsychological Test Automated Battery*** **(CANTAB**): The CANTAB provides a computerised series of tasks using a touch screen. The measures described here have formed the basis of numerous publications and further details regarding the different tasks and procedures used may be gained from these publications (Morris et al., 1988; Owen, Downes, Sahakian, Polkey, & Robbins, 1990; Owen, Doyon, Dagher, Sadikot, & Evans, 1998; Owen et al., 1993b).

- ***Motor screen:*** This task was used prior to the presentation of the CANTAB tasks to familiarise participants with the touch screen. In this task a series of crosses were presented in different locations on the screen. The participant was required to touch each cross when they appeared as quickly as they could.

- ***Stockings of Cambridge*** **(SOC's):** Based on the Tower of Hanoi (Shallice, 1982), the SOC's is considered to be a spatial planning task, requiring the formulation and execution of a series of sub-goals to complete simple problems. In this task the participant was shown two displays of three coloured balls, one in the top half of the screen and the other in the bottom half of the screen.



The balls were held in pockets or stockings, suspended from a line. Each pocket was a different size, one could hold only 1 ball, another a maximum of 2 balls and the third held a maximum of 3 balls (see above diagram which is an example from the CANTAB program). The participant was required to rearrange the balls in the bottom half of the screen to match the arrangement of the colored balls in the top half of the screen. A touch sensitive screen enabled the balls to be moved by the participant who selected the desired ball by touching the image of the ball on the screen and then touching an empty pocket space where they wanted to place the ball. The task started with a number of practice problems to familiarise the participant with the task (four 1 move problems and two 2 move problems). Individual problems were discontinued if the participant was unable to reach the solution in double the minimum number of moves plus one. There were a total of 12 problems that varied from two to five moves for a solution. If a participant was unable to solve three consecutive problems in the minimum number of moves, the task was discontinued. To gain a measure of movement speed, the computer replayed the solutions made by participant one move at a

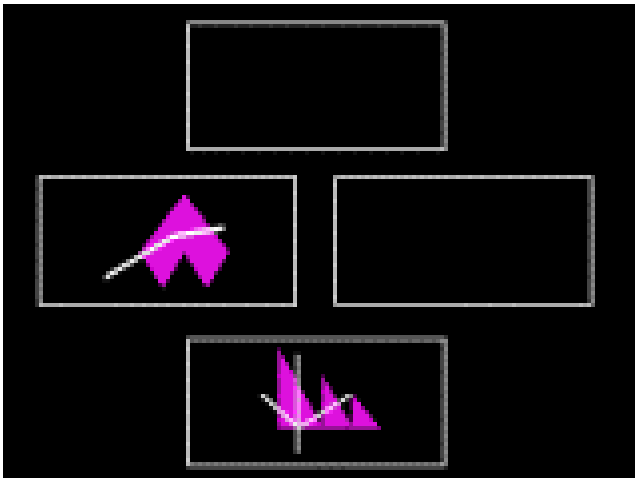
time, and the participant was required to copy the replayed moves. This occurred after the first six problems, and again at the end of the task. Correctly completed solutions were measured in terms of problems completed in the minimum number of moves, the number of moves required to complete a problem, time taken to plan the solution and time taken to execute the solution.

- ***Spatial Span:*** The CANTAB spatial span task is a computerised version of the Corsi Block tapping task (Milner, 1971). In this task a pattern of white boxes appeared on the screen. Some of the boxes changed colour for a brief period to indicate a sequence. The participant was required to remember which boxes changed colour as well as the order in which they changed colour. After a brief delay, the participant was required to touch the boxes in the same order that they changed colour. Sequences varied in length from 2 to 9 boxes. If the participant failed to remember the sequence correctly, another trial at that level was given. If the participant failed to remember the correct sequence on three trials at the same level, the task was discontinued. Spatial span was determined by the longest sequence correctly remember by the participant.

- ***Spatial Working Memory*****:** Participants were required to find a blue token hidden in a group of boxes without looking in a box more than once. Boxes were opened by touching each one so that it revealed its contents. Once the token was found, the participant used it to fill an empty column on the side of the screen. Then a new token was hidden in a different box and the participant searched again. The process was repeated until all the boxes had been used to hide the token and the column at the side of the screen was filled. There were 4 practice trials, each with 3 boxes, and then the test trials that included four trials each with 4, 6, and 8 boxes. An overall score was reported for each trial set, and the

total number of empty boxes visited before the blue token was found. In addition, two types of search errors were reported: if the participant returned to a box that had already been used to hide the blue token (a between search error), or if a participant returned to a box that had already been shown to be empty in the same search sequence (a within search error).

- ***Inter Dimensional/ Extra Dimensional Shift (ID/ED):*** This task was completed in two phases. During Inter Dimentional phase the participant was required to attend to specific attributes of a dimension presented on the screen and to shift attention to different attributes of the stimuli when required. Two dimensions were used, filled colored shapes and white lines (see picture below).



To begin with, two stimuli were presented on the screen, and the participant had to determine which was correct and which was incorrect and respond by touching the computer screen. After each response, the participant was given feedback to tell them whether their response was correct or incorrect. After six correct responses the stimulus and/or rules were changed. The term interdimensional was used to indicate that during this stage of the task the color filled shapes were the only relevant dimension. During the Extra

Dimensional phase (ED), the participant was required to stop attending to the previously correct dimension and respond to a dimension that was previously irrelevant. Therefore, instead of the color filled shapes being relevant, the white lines now become the dimension that needed to be attended to. The test was discontinued if the participant failed to meet the stage criterion after 50 trials. There were nine stages in total, and the ID/ED was scored according to stages completed and the number of trials taken to complete a stage, with higher scores indicating greater impairment.

6. ***CLOX*** (Royall, Cordes, & Polk, 1998)**:** The CLOX is a brief drawing task that assesses visuospatial/executive skills and is frequently used to screen for dementia (Royall, Cordes, & Polk, 1998). The test was administered in two stages, an unprompted stage and a copy stage. In the unprompted stage, the participant was given a blank piece of paper and instructed: "Draw me a clock that indicates 1:45. Set the hands and numbers on the face so that a child could read them." The copy stage required the participant to reproduce a clock that was first drawn by the examiner. Each stage of CLOX was scored from 0-15, with lower scores reflecting greater impairment (Royall, Cordes, & Polk, 1998). A cut off of 10 was used to distinguish normal elderly from those suffering from Alzheimer's disease (Royall, Mulroy, Chiodo, & Polk, 1999). A recent review of studies using the CLOX reported a high inter-rater reliability and sensitivity and specificity, and has also been reported as correlating highly with the MMSE (Shulman, 2000).

7. ***Continuous Performance Test*** adapted from (Adapted from Conner, 1995): This task was used to assess sustained attention. Stimuli for this test were computer generated. The participant was presented with a random series of letters on a

screen at varying inter-stimulus intervals of 2, 3 or 4 seconds. Each letter was displayed for 2 seconds. Participants were required to respond to each letter as quickly as possible by pushing the space bar. However, there was an exception to this rule; participants were told not to push the space bar when letter X appeared. The task was 4 minutes in duration. Two scores were generated using this task, the number of correct responses and the number of incorrect responses generated within each 1 minute period.

8. ***Daneman Carpenter Reading Span Test*** (Daneman & Carpenter, 1980): This test was used to assess the participant's verbal working memory (Waters & Caplan, 1996b) and involved the presentation of sets of 2 - 6 sentences, each consisting of 8 to 13 words. Testing began with sequences of two sentences, with there being 60 sentences in total. Participants were asked to read each sentence out loud, judge the veracity of the statement, and remember the last word in each sentence. At the end of each set the participant was asked to recall as many of the last words as possible. The reading span was the maximum sentence set remembered with over 66% accuracy (two out of three trials correctly recalled). The test is discontinued if the participant was unable to remember the last word from any of the sentences in a given trial.

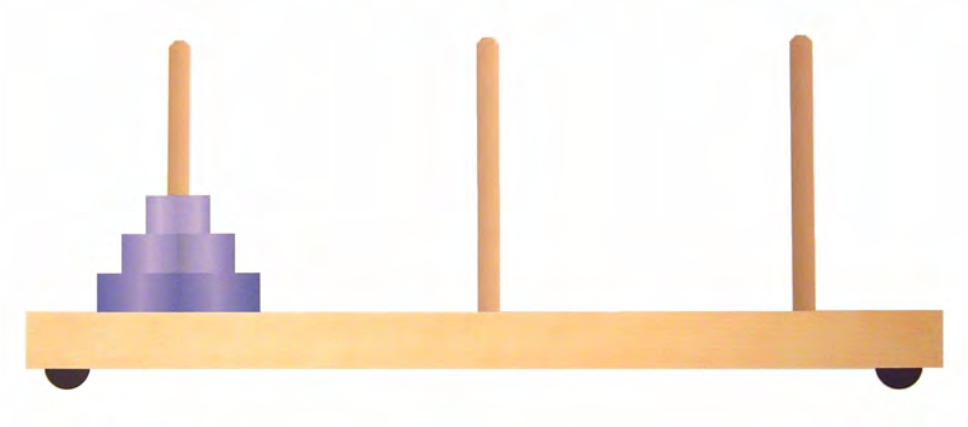
9. ***Delis Kaplan Executive Functioning System*** **(D-KEFS)** (Delis, Kaplan, & Kramer, 2001): The D-KEFS provides a battery of standardised tests designed to measure verbal and non-verbal executive functions. Five of the nine sub-tests were selected for use in this study. All sub-tests were administered according to standardised procedures outlined in the administration manual. For each subtest, raw scores were converted to age corrected scaled scores (mean = 10 and SD=3).

- ***Card Sort***: This was used to assess the participants problem solving ability and consisted of two conditions: a free sorting condition and sort recognition. In the first phase, the free sorting condition, participants were required to sort a set of 6 cards that had both perceptual features and printed words, into two groups, with three cards per group. Participants were required to generate as many different groups as possible using a different rule or concept for each sort. There were eight possible sorts. However, no feedback was given as to whether the sort was correct or incorrect. In the second phase, sorting recognition, the examiner arranged the cards into two groups, with three cards in each group, using the eight correct sorts from phase one. At the end of each sort the participant was required to describe the sorting rules that the examiner had used.

- ***Verbal Fluency*:** Designed to test an individuals' speed and ease of verbal speech, this test consists of three conditions, Letter Fluency, Category Fluency, and Category Switching. Letter Fluency required the participant to generate as many different words beginning with a given letter, excluding proper nouns, numbers and repetitions. Participants were given 60 seconds for each of three letters, F, A and S. In Category Fluency the participant was required to produce as many words as possible associated with a particular semantic category (animals and boys names were used in this study). The participant was given 60 seconds for each category. The third condition, category switching, required the participant to switch between two semantic categories (Fruits and furniture were used in this study). Production of words for each condition was measured in 15 second intervals in terms of the number of words correctly generated, preservations, and the ability to stay with the required category.

- ***Design Fluency*:** This test was originally developed as a non verbal equivalent to verbal fluency tasks. For this task the participant was presented with an array of boxes each containing 5 dots that they were required to connect, using only four lines, while making a different design each time. Each line had to be connected to at least one other line at a dot. For each of three conditions, Filled dots, Empty dots only and Switching, the participant was required to generate as many different designs as possible in a 60 second period. For the filled dots condition, each of the response boxes contains just 5 dots. The participant was asked to make as many different designs using just four lines to connect the dots. In the Empty dot condition, each response box had five filled dots and five empty dots, and the participant was asked to make as many different designs as possible using only four lines and only connecting the empty dots while ignoring the filled dots. In the final condition, Switching, each response box has five filled dots and five empty dots, and the participant was asked to make as many different designs as possible using just four lines and switching between an empty dot and a filled dot.

- ***Tower Test:*** This test has traditionally been used to assess problem solving skills associated with frontal deficits (Shallice, 1982). The D-KEFS tower test consists of five disks which vary in size from large to small, and a board with three vertical pegs of equal size (see picture below). For each of the nine problems, the participant was presented with an example of the tower to be built and two to five disks on the board in a predetermined starting position, depending on the level of difficulty of the tower. Participants were then told to move the disks on the board to look exactly like the tower in the picture.



They were asked to plan their moves prior to starting while observing two rules; never place a larger disk on top of a smaller disk and only move one disk at a time. Each problem was scored in terms of whether the participant was able to complete the tower, the number of moves made to complete the tower and time taken (bonus points were given for faster completion times). The task was discontinued after failure to complete three consecutive towers in the allotted time.

- ***Color-Word Interference Test*:** This test measured the individuals' ability to inhibit automatic verbal responses. Participants were required to respond to four separate conditions. In the first condition, the participant was presented with a page that had rows of coloured patches that they were required to name, and in the second condition they are presented with a page with rows of words that they were required to read. The third condition is the traditional "stroop effect" where the participants' were presented with a page of words printed in dissonant ink colours. Participants were asked to name the colour of the ink that the letters are printed in rather than reading the word. In the fourth and final condition, participants were presented with a page with rows of words, again printed in dissonant ink colours, but in this condition some of the words

are in boxes. The participant was required to name the colour of the ink for the words that are not in boxes, and read the word if the word is inside a box. For each condition participants were required to name the colours or read the words as quickly as possible without skipping any or making any mistakes.

10. ***Dementia Rating Scale-2*** **(DRS-2)** (Jurica, 2001): The DRS-2 is brief screen of impaired cognitive functioning, consisting of 36 tasks and five subscales. The five subscales provide information on specific abilities and include: 1. Attention; 2. Initiation/Perseveration; 3. Construction ability; 4. Conceptualisation; and 5. Memory. Based on normative data, raw scores from each subscale were summed to provide an over all score (scaled scores for each sub-scale range from 2-18, with higher scores indicating better performance). A combined scaled score was then generated adjusted for age and education using a regression formula provided in the administration manual (Jurica, 2001). This scale has been shown to differentiate between cognitive deficits in PD patients and healthy controls (Brown et al., 1999).

11. ***Digit Symbol Coding/Motor Copying (WAIS-III)*** (Wechsler, 1997): In this task participants were given an A4 sheet of paper. At the top of the page was a key consisting of nine boxes with a digit at the top of each box and a symbol at the bottom. Below these were lines of boxes with a digit at the top and an empty space at the bottom. Participants were given 180 seconds to accurately fill in as many empty spaces as possible by drawing the symbol in the bottom of the box that was associated with number at the top of the box using the examples from the top of the page. There were 133 boxes in the test. Each correct response was scored 1, and one point is deducted for every incorrect response. Raw scores

were converted to T-scores for all subtests, and are converted to age adjusted scores (mean=100; SD=15).

12. ***Fatigue Severity Scale*** (Krupp, LaRocca, Muir-Nash, & Steinberg, 1989): Based on the fatigue severity scale suggested by (Krupp, LaRocca, Muir-Nash, & Steinberg, 1989), this self-report questionnaire consists of 9 items relating to fatigue. Participants answer each of the items using a 7 point scale where 1 indicates strongly disagree and 7 strongly agree. For this study, participants were required to answer the nine questions, firstly in relation to mental fatigue, and then answer the same nine questions in relation to physical fatigue. Scores from the two scales were combined and ranged from 18-126, with higher scores indicating that the participant experienced higher levels of fatigue.

13. ***Frontal Systems Behaviour Scale*** **(FrSBe)** (Grace & Malloy, 2001): The FrSBe provides a measure of three areas of behavioural functioning: apathy, disinhibition and executive functioning. The test was a self report measure consisting of 46 questions describing possible behaviours, with each question being answered using a 5 point scale (1 = almost never and 5 = almost always). There was also a family rating form that enabled collateral information to be gathered from a person who knew the participant well. Each question was answered in terms of how the participant was "at the present time" and how they were "before illness or injury". Participants with PD were required to fill in both parts of the form, whereas controls were only required to fill in the questions relating to their current functioning. Raw scores were converted to age, gender and education adjusted T-scores (mean =50; SD=10). Detailed scoring is provided in the administration manual (Grace & Malloy, 2001). The

questionnaire has been reported to have good construct validity (Stout, Ready, Grace, Malloy, & Paulsen, 2003).

14. ***Functional Activities Questionnaire*** **(FAQ)** (Pfeffer, Kurosaki, Harrah, Chance, & Filos, 1982): The FAQ was designed to assess older adults on a set of complex higher order functional abilities. The questionnaire was completed by someone who knew the individual well. The informant was required to rate the participants ability to do each of the 10 tasks listed by ticking the box for the word or phrase that applies best using a 4 point scale (dependent = 3, requires assistance = 2, has difficulty but does by self = 1, no difficulty = 0). A total score for the FAQ was obtained by summing the scores across the 10 items. A score of 3 or "dependent" on three or more items is recommended as a cut-off for dementia (Pfeffer, Kurosaki, Harrah, Chance, & Filos, 1982). The scale has high sensitivity (0.85) and specificity (0.81) for distinguishing between demented and non-demented individuals (Pfeffer, Kurosaki, Harrah, Chance, & Filos, 1982).

15. ***Gambling Task*** (Bechara, Damasio, Damasio, & Anderson, 1994; Bechara, Damasio, Tranel, & Damasio, 1997): The Gambling task is considered to simulate real-life decision making. In this computer generated task participants were presented with four decks of cards, labelled A, B, C, and D. The order of cards was predetermined and each deck had a different schedule of rewards and punishment. Participants were required to select a card, from any deck, by clicking on it to reveal either a reward (increase in money) or punishment (decrease in money) with the instruction to win as much money as possible, or to avoid losing as much as possible. A green bar at the top of the screen indicated how much the participant had won. Participants began the game with a $2000.00 credit. Overall, decks A and B were disadvantageous

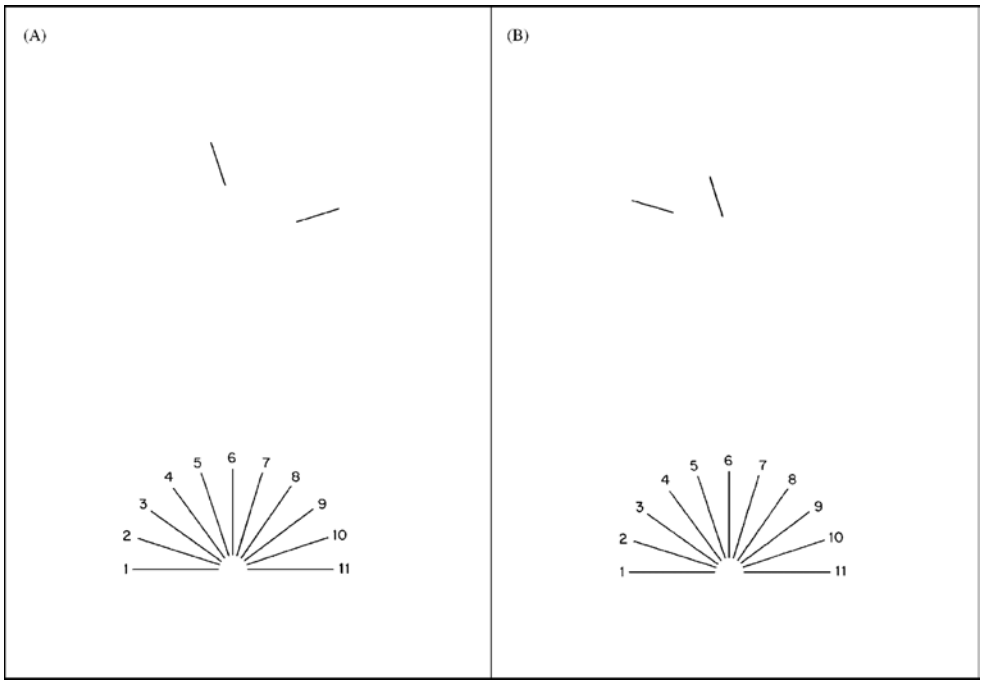
(large gains but bigger losses) and decks C and D were advantageous (small gains but smaller losses). Most people learn this pattern of wins and losses after approximantely 40-50 selections. However, research indicates that patients with orbito frontal cortex lesions (also implicated in PD) tend to perseverate with bad decks (Bechara, Damasio, Damasio, & Anderson, 1994). There were 60 cards in each deck, and participants were required to continue playing until a total of 100 cards had been used. Scores were calculated by the number of advantageous choices (C+D) minus disadvantageous choices (A+B) over the 5 blocks of 20 cards, and for the total 100 cards.

16. ***General Health and Demographic screen:*** In addition to demographic data, specific questions regarding the particpants' health history were gathered. The general health questionnaire included questions related to the inclusion/exclusion criteria, years of education, caffeine use and alcohol and drug use.

17. ***Geriatric Depression Scale (GDS)*** (Yesavage et al., 1982): The GDS is a self report scale used to screen for possible depression in a normal older population. This scale is considered as more appropriate for use with older populations as it does not contain questions pertaining to somatic symptoms. The scale consists of 30 yes/no items that assess an individual's mood over the previous one week period. Items are scored as present or absent (0 = absent; 1= present) with total scores ranging from 0-30. A score of 0-9 is considered normal, 11-20 mild to moderate depression and over 20 indicative of severe depression (Brink & et al., 1982). This scale has been validated for use with PD patients (Ertan, Ertan, Kizilatan, & Uygucgil, 2005).

18. ***Hospital Anxiety and Depression Scale*** **(HADS)** (Zigmond & Snaith, 1983): The HADS is a brief 14 item self report measure of anxiety (7 items) and depression (7 items). It was developed for use with medical patients and is sensitive to mild disturbances in mood, without relying on somatic symptoms (Herrmann, 1997). Participants were asked to rate how they had been feeling in the past week using a 4 point scale (0-3) for both anxiety, and depression scales. The following recommended cut-offs were used, mild = 8-10, moderate = 11-15, and severe = 16 or above.

19. ***Judgement of Line Orientation (JOL)*** (Benton, Varney, & Hamsher, 1978): Judgement of Line Orientation test is frequently used to assess visuospatial function. Participants were presented with a booklet containing a series of card pairs. One of the card pairs, the response card, was displayed on the bottom of the page and contained an array of 11 numbered lines (3.8cm in length) each separated by an angle of 18 degrees (see picture below).



The stimulus card was on the top page and displayed two lines at different angles

(3.8cm for practice items and 1.9cm in length for test items). The participant was asked to identify the orientation of two lines on the bottom card by identifying the two lines with the same orientation from the 11 line array (see above drawings (A) and (B) for examples). Each participant was presented with 5 practice items and 30 test items. Responses for each line pair are scored 0 for an incorrect response and 1 for a correct response.

20. ***Memory for Temporal Word Order-Time One*** (Shimamura, Janowsky, & Squire, 1990): This test consisted of 15 single syllable words printed individually on cards (5.5cm x 12.5cm). The participant was instructed to read aloud each word, presented to them by the examiner at the rate of 1 per second, and remember the sequence in which they occurred. After a 10 second delay, using a duplicate set of cards, the participants were presented with an array of the same words in a different order and asked to place the words in the same order as the first list. The ability to remember the sequence in which the cards originally appeared is scored for each participant using Spearman rank order correlation (Shimamura, Janowsky, & Squire, 1990). A higher correlation indicates greater accuracy in remembering the word order (100% accuracy = +1.0).

21. ***Memory for Temporal Word Order Revised*** (Shimamura, Janowsky, & Squire, 1990): This test is identical to the Memory for Temporal Word Order test administered at time one. However, the number of test stimuli was reduced to eight words to over come the floor effects that were evident for older individuals during the first testing session.

22. ***Mini Mental Status Exam (MMSE)/Modified MMSE (3MS)*** (Folstein, Folstein, & McHugh, 1975; Tombaugh, McDowell, Kristjansson, & Hubley, 1996): The MMSE is a brief objective screening instrument for the assessment of current

cognitive status, consisting of items that test an individual's orientation to time and place (10 points), registration, attention and short-term memory (11 points) and language (9 points). Items were scored as correct or incorrect. Scores ranged from 0-30, with lower scores indicating greater impairment. A variety of cut offs have been suggested for this instrument, but scores below 23-24 have been reported as having high sensitivity and specificity in identifying individuals with dementia (O'Connor et al., 1989). For this study, a score of ≥ 25 was defined as "no signs of overt dementia" as part of the initial exclusion criteria. The additional 4 categories (date and place of birth, word fluency, similarities, delayed recall of words) used in the 3MS were also administered and scored according to standard guidelines (Teng & Chui, 1987). Scores for the 3MS range from 0-100 with lower scores indicating greater deficits. A cut off score of <78 is considered sensitive for detecting early signs of Alzheimer's disease (Tombaugh, 2005).

23. ***Modified Hoehn and Yahr*** (Hoehn & Yahr, 1967): The modified Hoehn and Yahr scale is a widely used descriptive staging scale for PD patients. This scale requires direct examination of the patient. A numeric rating of 0-5 is used to represent increasing severity of symptoms, where 0 represents no sign of the disease and 5 represents wheel chair bound or bedridden unless aided. In this study, the modified version of this scale which uses increments of 0.5 in the midranges was used. It has been reported that the progression on the Hoehn and Yahr scale correlates well with motor decline, making it a useful measure for defining inclusion/exclusion, and has been reported as having good validity and reliability (Ramaker, Marinus, Stiggelbout, & Van Hilten, 2002).

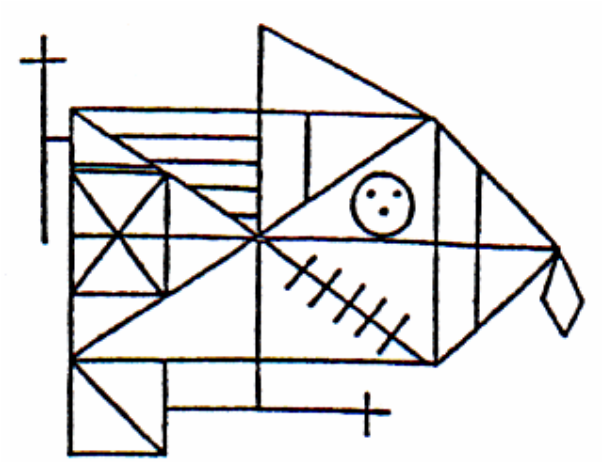
24. ***Motor Copying (WAIS-III)*** *(Wechsler, 1997)*: This task is used in conjunction with the Digit Symbol Coding task (see test 11) and follows a similar format. Participants were presented with an array of boxes on a page. In the top of each box was a symbol which the participant was required to copy in the empty space at the bottom of the box. Each correct response was scored 1, and 1 point is deducted for every incorrect response. The total score was then be subtracted from the Digit Symbol Coding score to provide an overall score for processing speed that was corrected for motor speed.

25. ***National Adult Reading Test (NART):*** This test provides a brief estimate of full-scale IQ and comprises of a list of 50 "irregular" words (e.g Psalm) printed in order of increasing difficulty. The words are "irregular" in terms of their pronunciation to minimise the possibility of reading by phonemic decoding rather than word recognition. Words are scored 0 for incorrect pronunciation and 1 for correct pronunciation. Raw scores are then converted to estimated premorbid IQ scores (instruction on how to calculate these transformations are contained in the instruction manual) (Nelson & Willison, 1991). Correlations between NART IQ scores and more comprehensive batteries used to assess intelligence such as the WAIS and WAIS-R, are between 0.72 -0.81 (Lezak, 1995).

26. ***Neuropsychiatric Inventory (NPI)*** (Cummings et al., 1994): The NPI is based on a structured interview with a caregiver who knows the patient well, and is designed to assess psychopathology associated with dementia. The interview covers 12 different areas of behavioural functioning: 1. delusions, 2. hallucinations, 3.Agitation, 4. depression, 5. anxiety, 6. euphoria, 7. apathy, 8. irritability, 9. disinhibition, 10. aberrant motor behaviour, 11. night-time behaviour and 12. appetite/eating change. Each question addresses changes in the person's

behaviour since the onset of the illness. The caregiver is first asked whether the behavioural change is present or absent. If it is absent the interviewer continues to the next question. If the behaviour change is present, the interviewer asks about the frequency (1 = occasionally - less than once per week, 2 = often-about once per week, 3 = frequently-several times per week but less than everyday, 4 = very frequently – daily or essentially continuously present) and severity (1 = mild – produces little distress in the patient, 2 = moderate – more disturbing to the patient but can be redirected by the caregiver, 3 = severe – very disturbing to the patient and difficult to redirect) of the behaviour. Each domain is also scored in terms of how emotionally distressing the caregiver finds the behaviour (0 = no distress, 1 = minimal, 2 = mild, 3 = moderate, 4 = moderately severe, 5 = very severe or extreme). Four scores were generated for each domain, frequency, severity, total (frequency x severity) and caregiver distress. The scale has been reported to have good content and concurrent validity and inter-rater reliability (Cummings, 1997).

27. *Rey Osterrieth Complex Figure Test* (ROF) (Lezak, 1995): This test assesses a number of skills including planning, organisation and visuoconstructional ability



and memory. The participant was first asked to copy a complex figure (the Rey figure was used in this study, see above drawing) as carefully as possible. Then after a 2½ minute delay and again after a 30 minute delay, without prior warning, participants were asked to reproduce the figure from memory. Each of the three figures produced is scored separately on 18 different scoring units. Each unit receives a score between 0-2 and is considered both in terms of accuracy and position relative to the whole design. Total scores range from 0-36. This test has previously been reported as sensitive to deficits in PD (Freeman et al., 2000).

28. *Test of Everyday Attention* (TEA) *Map Search* (Robertson, Ward, Ridgeway, & al., 1994): The map search is one sub-test of the TEA and is a visual search task which assesses visual selective attention. Participants were presented with a map that had a number of different symbols (target symbols and distracter symbols) and were required to ring as many target symbols as possible in a two minute period. On the desk beside the participant was a cue to remind them which symbol they were searching for. After one minute participants were required to switch pens to enable a score for one minute to be obtained as well as a total

score. Each correctly circled symbol was scored with a 1 and raw scores were then converted to age adjusted percentile score as outlined in the test manual (Robertson, Ward, Ridgeway, & al., 1994).

29. ***Test of Language Competence- Expanded Edition*** **(TLC-E):** The TLC-E level two assesses higher order language functioning. Explicit scoring instructions for this test are provided in the test manual (Wig & Secord, 1989). Four areas of language competence were assessed and included:

- ***Ambiguous Sentences*****:** Participants were first read an ambiguous sentence that was then displayed in print. For example "I saw the girl take his picture". They were then asked to provide two correct meanings for the sentence. A total of 15 sentences are presented, two trial sentences and 13 test sentences. A score of 0 was given for no correct responses, 1 for one correct response, and 3 when the participant identified both correct responses.
- ***Listening Comprehension*** **(making inferences):** For the second sub-test participants were first read a scenario that is displayed in print. For example, "Eric had wanted a moped for the longest time. He sure was grateful for his Uncle Fred. Eric was grateful for Uncle Fred because…". Participants were then read four statements, provided in print at the bottom of the page, and asked to select two plausible inferences for the scenario. A total of 13 sentences were presented in this manner (one trial sentence and 12 test sentences). A score of 0 was given for no correct responses, 1 for one correct response, and 3 if the participant identified both correct responses.
- ***Oral Expression*** **(recreating sentences):** For the third sub-test participants were presented a picture of a scene and read a sentence. At the top of the picture were three words. The participant was required to create an appropriate sentence that

could be used in the situation using all three words. Two trial sentences and 13 test sentences were presented. All responses were recorded verbatim and were scored for inclusion of target words, 0 for one or no target word, 1 for any two words, and 3 points for all three words. Sentences were also scored in terms being semantically, syntactically and pragmatically correct. Intact sentences were given a score of 3 points, sentences with minor deviations 1 point, and 0 points allocated for major deviations that result in nonsensical, "bizarre" or fragmented sentences.

- ***Figurative Language*:** This sub-test is made up of two tasks. In task A participants were verbally presented a situation and a figurative expression related to the situation. Both the description of the situation and the figurative expression were also presented in print. They were then asked to provide an interpretation for the figurative expression, which was recorded verbatim. In task B participants were asked to match the figurative expression to one of four choices. The situation description, figurative expression and the four choices were all presented in print. The test consisted of one trial and 12 test items. A score of 0 was given if the participant was unable to give an accurate interpretation or select the correct matching expression. A score of 1 was given if the participant could give either an accurate interpretation or select the correct matching expression, and a score of 3 if they complete both tasks A and B correctly. For each of the sub-tests the discontinue rule of failure to respond to three consecutive items was used.

30. ***Theory of mind test*:** Based on a test that was devised to assess how well the participant was able to interpret the complex mental states of others (Baron-Cohen, Wheelwright, Hill, Raste, & Plumb, 2001). Participants were presented

with a partial picture of a face showing only the eye-region, and at each corner of the picture was a word. They were then asked to make a judgement about which of four words most closely matched what the person in the picture might be thinking or feeling. On an adjacent page was a description for each word. Participants were shown one practice item, to ensure they understood the task, and 36 test items. Items were scored 0 for incorrect choices and 1 for correct choices.

31. ***The Clinical Assessment of Fluctuation*** (Walker et al., 2000): This scale is a brief screening instrument to assess whether an individual is experiencing episodes of confusion or impaired consciousness. Episodes of confusion or impaired consciousness are infrequent in the normal population and may indicate the onset of dementia (Walker et al., 2000). An informant, who knew the participant well, was asked a series of questions regarding episodes of confusion or impaired consciousness that had occurred in the month prior to assessment. If there had been any episodes of confusion or impaired consciousness, the informant was asked to rate these using a 4 point scale. For periods of confusion the informant was asked about frequency (1 = one per month, 2 = monthly-weekly, 3 = weekly-daily and 4 ≥ daily), and for impaired consciousness the informant was asked about duration (0 = seconds, 1 ≤ 5 minutes, 2 = 5 minutes-1 hour, 3 ≥ 1 hour and 4 ≥ 1 day). These two scores were then multiplied together to produce a severity score that ranged between 0-12, with 0 representing no fluctuation or confusion and 12 being indicative of severe fluctuating confusion (Walker et al., 2000). The authors of this test indicate that a score of 16, although possible, would indicate a state of continuous confusions and therefore would not be indicative of fluctuation (Walker et al., 2000).

32. ***The Adaptive Digit Ordering Task (DOT-A)*** (Werheid et al., 2002).The DOT-A is working memory task that is conceptually and structurally similar to traditional digit span tasks. However, the DOT-A has been reported as having greater sensitivity to deficits associated with PD (Werheid et al., 2002). Participants were verbally presented a random string of numbers and required to repeat them back in ascending order. Each number was presented at the rate of one per second and strings varied in length from 3 to 8 items. There were six different span lengths and two trials were given for each span. The test was discontinued if the participant failed both trials of any item. Each trial was scored 1 for correct and 0 for incorrect. The maximum number of digits and letters ordered correctly was reported.

33. ***The Executive Interview (EXIT 25)*** (Royall, Mahurin, & Gray, 1992): The EXIT25 consists of 25 test items to assess frontal systems impairment, and includes tests of perseveration, imitation, intrusions, frontal release signs, spontaneity, disinhibition and utilization behaviour. Scores range from 0-50, with higher scores indicating greater impairment. A cut off of 9 ± 3 is recommended as discriminating non-demented community dwelling elderly, with a cut off of 15 as discriminating normal elderly from those with dementia (Royall, Mahurin, & Gray, 1992).

34. ***The Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE)*** (Jorm, 2004): The IQCODE assesses both positive and negative changes in memory over a 10 year period. Informants are asked to rate the "significant other on 16 statements compared with how they were 10 years ago using a 5 point scale where 1 = much improved and 5 = much worse. Scores ranged from 16 to 80 with higher scores being indicative of greater impairment. However, this scale is

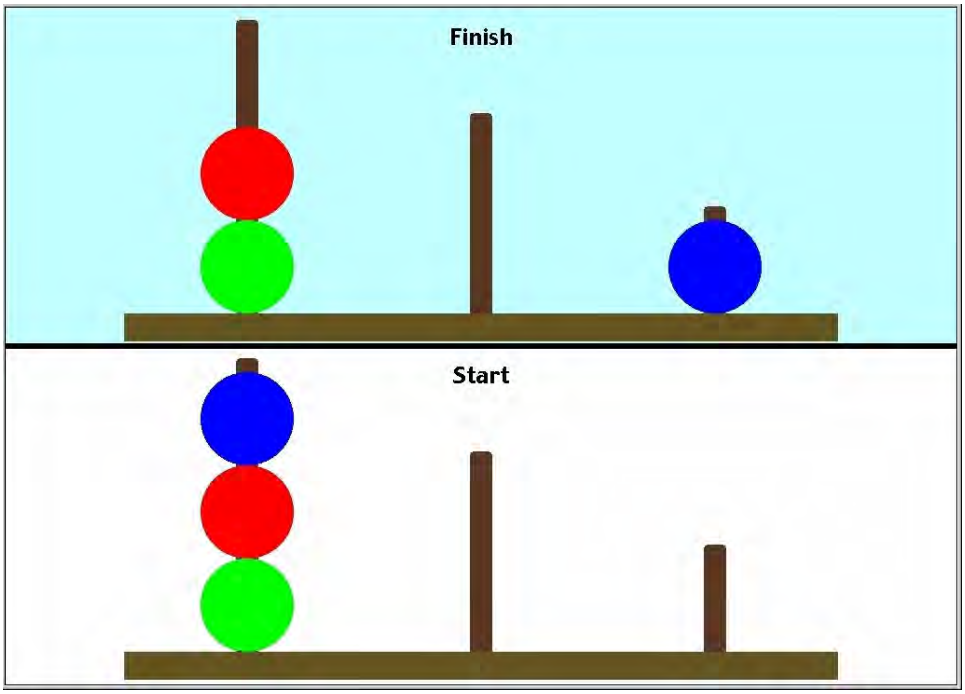
unique as it is possible for an individual to have improved over the 10 year period and scores under 48 indicated that there had been a general improvement in memory. A systematic review of research using this measure indicated that it had high reliability for measuring cognitive decline (Jorm, 2004).

35. ***The One Day Fluctuation Assessment Scale*** (Walker et al., 2000): This scale was used in conjunction with The Clinical Assessment of Fluctuation and was only administered if the informant had indicated that the individual they were rating had experienced periods of confusion or impaired consciousness. Using this scale, the informant was asked to rate the "significant other" over the previous 24 hours on seven items consistent with confused behaviour (falls, fluctuation, drowsiness, attention, disorganised thinking, altered level of consciousness, communication difficulties). Scores range from 0-21 with higher scores being indicative of greater impairment (Walker et al., 2000).

36. ***The Parkinson's Disease Questionnaire*** **(PDQ-39)** (Jenkinson, Fitzpatrick, & Peto, 1998): The PDQ-39 is a 39 item self-report questionnaire developed to assess the impact of PD on an individual's daily life. The questionnaire is comprised of eight scales: 1. Mobility (10 items), 2. Activities of daily living (6 items), 3. Emotional well-being (6 items), 4. Stigma (4 items), 5. Social support (3 items), 6. Cognitions (4 items), 7. Communications (3 items), 8. Bodily discomfort (3 items). Participants were asked to indicate the extent to which each of the 39 questions had applied to them over the previous month, using one of five response categories: never, occasionally, sometimes, often, and always or cannot do at all. Using the formula supplied in the manual, each scale was calculated to range from 0, no problem at all, to 100, maximum level of problems. A single index score was calculated by summing the eight scales and dividing by 8. The

PDQ is reported to have good test-retest reliability and good content and construct validity (Marinus, Ramaker, van Hilten, & Stiggelbout, 2002).

37. ***The Tower of London Task Revised (TOL-R):*** The TOL-R is a computerized Tower of London task used to assess planning ability and consisted of a custom designed computer program on a Macintosh G4 running OS9 with an ELO 17 inch touch sensitive monitor having a screen resolution of 1280 by 1024 pixels. The screen comprised two Tower of London images, one in the top half of the screen, the model or finish state, and one in the bottom half, the start state. Only balls in the bottom half of the screen could be moved and the background of the top half of the screen was colored to remind participants of this rule (see picture below for an example of the customised TOL-R (McKinlay et al., In Press).



At the side of the screen a number indicated how many moves were required to solve the problem. Participants interacted with the computer task by touching an on-screen ball to select it. When selected, the ball's circumference flashed and the computer

emitted a sound, the participant could then place the ball onto another tower by touching the tower, or unselect the ball by touching it again. Three primary measures were obtained using this task, pre-planning time, time to complete the task and number of moves to complete the task. A total of forty one problems were administered divided into 2 phases. Phase one of the computerized task consisted of 16 practice problems (2x1 move problems, 2x2 move problems and 12x3move problems). Each problem in this section had a time limit of 60 seconds. Participants were required to complete 92% (11) of the problems in this phase in order to progress to phase two. Phase two was divided into two parts. Part A consisted of 9 problems (3x3 move problems, 3x4 move problems and 3x5 move problems). Problems in this part of phase two had a time limit of 120 seconds. This phase was discontinued if the participant failed three consecutive tower problems. Phase two part B consisted of 16 problems (8x5 move problems and 8x6 move problems). Problems in this part of phase two had a time limit of 180 seconds. This phase was discontinued if the participant failed three consecutive tower problems. For failed problems (either timed out or over the maximum number of moves) or problems that were not attempted, participants were assigned the maximum number of moves plus 1 and the maximum allowable time.

38. ***Unified Parkinson's Disease Rating scale (UPDRS):*** Developed by Fahn & Elton (1987), the UPDRS is a 42 item clinical test designed to provide a measure of the signs and symptoms associated with PD. The UPDRS is structured according to four sections; 1. Mentation, behaviour and mood (e.g., cognition and motivation); 2. Activities of daily living (e.g., speech, dressing and hygiene); 3. Motor examination; 4. Complications of therapy (e.g., presence of dyskinesias, and fluctuations in medication effectiveness). Sections one, two and four are gathered by interview and section three by direct examination. The first three sections are

rated on a 4 point scale (0 = normal and 4 = severe presentation of symptom). The final section, complications of therapy, only 4 of the 11 items are rated on a 4 point scale with the remaining 7 being rated as present or absent (absent = 0 and present = 1). The UPDRS is reported as having high convergent validity (Martinez-Martin et al., 1994) and good interrater reliability (Fahn & Elton, 1987; Goetz et al., 1995; Ramaker, Marinus, Stiggelbout, & Van Hilten, 2002).

39. ***Visual Association Test (VAT)*** (Lindeboom, Schmand, Tulner, Walstra, & Jonker, 2002): The VAT is a test of incidental learning that consists of two sets of 6 line drawings. The participant was first presented with 6 line drawings of objects or cues (e.g., a chair) and was asked to name them; they were not told that the objects must be remembered. On the second presentation participants were presented with the same line drawings at a rate of 1 every 4 seconds, but this time the target was added in the form of an interacting object or animal (e.g. a hedgehog on the chair). As with the first presentation, there was no explicit instruction to memorise the drawings. On the third presentation participants were shown the original objects (cues) and asked to name the object that was missing (targets). If less than 6 items were recalled, the second and third steps were repeated. Items were scored 0 for incorrect and 1 for correct. If a participant recalled all 6 items on the first recall trial, they were given a score of 12. The VAT has been reported as have high specificity and sensitivity in distinguishing between dementia of the Alzheimer type (AD) and individuals without dementia using a cut off <4 for the first recall presentation (Lindeboom, Schmand, Tulner, Walstra, & Jonker, 2002).

40. ***Visual Object and Space Perception Battery (VOSP):*** (Warrington & James, 1991). The VOSP is a test of visual perception. Two sub-tests were used from this

battery, incomplete letters and the object decision test. Sub-tests were administered according to standard procedures. Prior to administration of the subtests participants completed a screening test to ensure adequate visual sensory capacities.

- ***Incomplete letters:*** Stimuli consisted of 2 practice letters degraded by 30% and 20 test letters degraded by 70%. Participants were presented with pictures of incomplete letters one at a time and asked to name them. Each answer was scored 1 correct, or 0 for incorrect, giving a maximum score of 20. The sub-test was marked pass/fail. Participants were considered to have failed if they score below the 5th percentile for their age range (<16 for individuals over 50).
- ***Object decision:*** This sub-test used silhouette drawings of objects. Participants were presented with 20 arrays of 4 silhouettes, in each array only 1 of the 4 objects was a silhouette of a real object, the other three were distractor items constructed from similar but imaginary shapes. Participants were required to identify the real object. Each answer was scored 1 correct, or 0 for incorrect, giving a maximum score of 20. The sub-test was marked pass/fail. Participants were considered to have failed if they score below the 5th percentile for their age range (<14 for individuals over 50).

41. ***Wechsler Abbreviated Scale of Intelligence (WASI)*** (Wechsler, 1999): Two sub-tests were used from this battery, Vocabulary and Matrix Reasoning. These two sub-tests provided an estimate of current Full Scale IQ. Sub-tests were administered according to standard procedures and raw scores were converted to age corrected T-scores (mean of 50 and standard deviation of 10).

- ***Vocabulary*****:** This sub-test assessed the individual's expressive language skills. The test consisted of a total of 42 orally presented items for which the participant

provided a verbal description. Items were scored either 0 for an incorrect description, 1 for a partially correct description, or 2 for a correct description. The test was discontinued after 5 consecutive scores of 0.

- ***Matrix Reasoning*:** The Matrix Reasoning sub-test consists of a total of 35 incomplete patterns of increasing complexity. The participant was required to complete each pattern by selecting the correct response from 1 of 5 choices. Each item was score 0 for a fail and 1 for a correct response. The test was discontinued after 4 consecutive scores of 0, or 4 scores of 0 on 5 consecutive items.

42. ***Wechsler Memory Scale 3rd edition (WMS-III)*** (Wechsler, 1997): A number of sub-tests were used from the WMS-III to assess the participants ability to learn and retain orally presented information. Raw scores for all sub-tests were converted to age adjusted scores (mean =100; SD=15). Detailed scoring is provided in the manual for these sub-tests (Wechsler, 1997). Each sub-test was administered according to standard procedures.

- ***Auditory Recall.*** This task is a test of delayed auditory recognition. Performance is based on the composite of the Logical Memory II and Paired Associates II delayed recall phase which are described in detail below. Raw scores vary between 0-30 and 0-24 for Logical Memory II and Paired Associates II respectively with higher scores indicating more complete recall.
- ***Logical Memory I & II***: Required both immediate and delayed recall of a narrative story. In the immediate recall phase the participant was orally presented two narrative stories. At the end of each story the participant was required to repeat back everything they heard. The second story was repeated twice. The delayed recall phase occured after an interval of between 25-30 minutes. The participant was once again required to recall everything they could

remember about the two stories. For this study, scores from Logical Memory I & II were summed to provide an overall score. Directly after completing the delayed recall phase, participants were asked 15 yes / no questions about each story**.**

- ***Paired Associates I & II*****:** This involved learning pairs of unrelated words so that the second word may be recalled when the first is presented. Participants were read a list of eight word pairs. After a delay of five seconds the first word in each pair was read and the participant was required to provide the second word. This sequence of presentation and recall was repeated over four trials. At the end of the final recall phase, participants were told to remember as many of the words as possible as they would be tested again. After an interval of between 25-30 minutes the participant was orally presented the first word in the pair and asked to recall the second word. For this study scores from Paired Associates I & II were summed to provide an overall score. Directly after completing the delayed recall phase, participants were read 24 word pairs and asked to identify, by answering yes/no, which word pairs were included in the list they had learnt.
- ***Letter-Number Sequencing test***: Participants were verbally presented a string of numbers and letters (e.g., 3-Y-7-G) that they were required to re-order starting with the numbers, from lowest to highest, and then the letters in alphabetical order (e.g., 3-7-G-Y). Strings varied in length from 2 to 8 items. The maximum number of digits and letters ordered correctly was reported.
- ***Digit Span***: There were two components to this sub-test, digits forward and digits backwards. In digits forward, participants were required to repeat back an increasing string of verbally presented digits (2-9 items). In digits backwards, the participant was required to repeat back in reverse order an increasing string

of verbally presented digits (2-8 items). Maximum number of digits repeated correctly was reported.

Chapter 3 - Neuropsychiatric Problems Associated With Parkinson's Disease

Abbreviations used in the text Chapter 3

1) **AUC =** Average Under the Curve; 2) **BDI-II** = Beck Depression Inventory; 3) **DSM-IV** = Diagnostic and Statistical Manual Fourth Edition; 4) **FrSBE** = Frontal Systems Behaviour Scale; 5) **GDS** = Geriatric Depression Scale ; 6) **HADS** = Hospital Anxiety Depression Scale; 7) **H&Y =** Hoehn and Yahr Staging Scale; 8) **MMSE =** Mini Mental Status Exam; 9) **NART** = National Adult Reading test; 10) **NPI** = Neuropsychiatric Inventory; 11) **PD** = Parkinson's disease; 12) **PDQ-39 =** The Parkinson's Disease Questionnaire; 13) **S&E =** Modified Schwab and England Activities of Daily Living Scale; 14) **UPDRS** = Unified Parkinson's disease Rating Scale; 15) **ROC =** Receiver Operating Characteristics.

3.1 Overview

Defining the range and frequency of neuropsychiatric problems in patients with Parkinson's disease (PD) has generated a great deal of interest over the past decade (e.g., Schrag, 2004; Schrag, Hovris, Morley, Quinn, & Jahanshahi, 2006; Shulman, Taback, Bean, & Weiner, 2001; Shulman, Taback, Rabinstein, & Weiner, 2002). This interest has partly been due to a rising awareness that PD patients frequently suffer from a range of neuropsychiatric problems which have frequently been overlooked by clinicians (Schrag, 2004; Shulman, Taback, Rabinstein, & Weiner, 2002). But also because, these problems are increasingly recognised as having an impact on quality of life for PD patients perhaps more so than the motor problems that has traditionally been the focus of any interventions. Moreover, neuropsychiatric problems have been found to impact on the caregivers' ability to cope (Schrag, Hovris, Morley, Quinn, & Jahanshahi, 2006). The latter point is extremely important as PD patients often require high levels of assistance especially as the disorder progresses and caregiver distress may result in premature rest home placement having personal, social and health care cost.

3.1.1 Difficulty with Research in the Area

Assessing functional deficits in PD patients that are related to neuropsychiatric problems poses a number of difficulties in addition to those discussed earlier in relation to cognitive deficits (see section 1.6.2). There are few neuropsychiatric tests specifically designed for or even validated for use with PD patients. Furthermore, the current literature uses self report and significant other report interchangeably despite the fact that there is currently no evidence to suggest that these represent interchangeable means of reporting neuropsychiatric problems.

3.2 Current Research

The investigation of neuropsychiatric problems for patients with PD partially addresses the first two objectives of this thesis (see section 1.14 for full outline of objectives for the thesis). An initial objective of the thesis was to identify some of the pertinent cognitive, behavioural and psychiatric deficits in PD patients compared to normal elderly. As part of this first objective an examination of the relative sensitivity of different measures for use with PD patients was also undertaken. The second objective was to assess the ability of PD patients to function efficiently in the environment when they had cognitive or neuropsychiatric problems. As part of this objective the possibility that neuropsychiatric problems would manifest in reduced quality of life was also examined.

3.2.1 Manuscript 1 – Quality of Life

To partially address the first and second objective, the first manuscript in this chapter examines the range of neuropsychiatric problems present in PD patients without dementia compared to healthy older individuals. Currently, there is little research that has examined the range of neuropsychiatric deficits associated with PD and much of what is known about these problems has come from studies which have focused on only a small number of possible problems (e.g., examining the frequency of single neuropsychiatric problems such as depression or anxiety). In this manuscript the relationship between neuropsychiatric problems and patients perceptions of their own quality of life was also examined. Outcomes from this part of the study indicated that neuropsychiatric problems were common for patients with PD. Moreover the presence of these problems was related to diminished quality of life as measured by the Parkinson's Disease Questionnaire (PDQ-39) (Jenkinson, Fitzpatrick, & Peto, 1998).

As a caveat to this first paper it is important to be aware that the general concept "Quality of Life" has been criticised as being poorly defined and somewhat subjective (McKevitt, Redfern, La-Placa, & Volfe, 2003). Further, many Quality of Life scales been found to have questionable psychometric properties (McKevitt, Redfern, La-Placa, & Volfe, 2003). The PDQ-39 has been designed and validated specifically for use with PD (Hagell, Whalley, McKenna, & Lindvall, 2003). The PDQ-39 is comprised of 39 questions which provide scores on eight discrete scales. These scales can also be combined to form a meaningful single summary score (Jenkinson, Fitzpatrick, & Peto, 1998). However, the eight scales are made up of varying numbers of items (e.g., 3 for Social support and 10 for Mobility) calling into question the validity of the eight separate scales. Further, some of the response alternatives have been found to be ambiguous (Hagell, Whalley, McKenna, & Lindvall, 2003). It has been suggested that this questionnaire, although promising for use with this population, still requires further refinement (Hagell, Whalley, McKenna, & Lindvall, 2003). Therefore, the outcomes reported here should be viewed with some caution.

3.2.2 Manuscript 2 – Self v Significant Other

The second manuscript in this chapter focuses on the degree to which informant and self-report can be considered to be interchangeable. This paper also examines the relationship between caregiver perceptions of neuropsychiatric problems for PD patients and their own level of distress. Results indicated that there is a high level of disagreement between significant other and self report. Furthermore, caregiver distress was correlated with caregiver perceptions of the neuropsychiatric problems.

This paper did not address the issue of which reporter was most accurate. This question would need to be addressed in a future study. However, it did confirm that

these reporting methods provided different information. One explanation for this could be that covert problems such as anxiety and depression are more identifiable by the person experiencing them whereas the frequency of overt behaviours associated with aggression maybe more accurately reported by an observer. Alternatively, there may be bias and inaccuracy in both types of report. For example, observer report may be seriously biased by their own levels of distress whereas patient report may be distorted by a lack of insight into their problems. To answer these questions future research could use more objective means of collecting information i.e impartial observers.

3.2.3 Manuscript 3 – Unified Parkinson's Disease Rating Scale

The third manuscript in this chapter compared the relative sensitivity of 3 different measures of depression (Beck Depression Inventory-II (BDI), Geriatric Depression Scale (GDS) and the Hospital Anxiety Scale (HADS)) and the Unified Parkinson's Disease Rating Scale (UPDRS). Presence of low mood or depression is often overlooked in PD patients (Shulman, Taback, Rabinstein, & Weiner, 2002). This aspect of the research was undertaken to examine how accurate the UPDRS, commonly used by clinicians, would be in identifying patients with symptoms consistent with at least low mood, and who might require further assessment. Results indicated that the UPDRS was not accurate, especially when identifying patients with only mild symptoms. It was therefore concluded that it would be appropriate for a brief scale such as the BDI-II or the GDS be used routinely to screen for depression.

One potential criticism of this study might be that the cut-offs for the BDI-II were validated for use with young healthy adults (Beck, Steer, & Brown, 1996), also that the BDI-II contains a number of items that tap into somatic problems. However,

we found a high level of agreement between the BDI-II and GDS, the latter which has been validated for use with older populations.

3.2.4 Summary

Overall evidence for a variety of neuropsychiatric problems was found for PD patients. This finding was consistent with other research in this area. Moreover, neuropsychiatric problems were found to negatively impact on the quality of live for PD suffers. While previous studies have gathered information regarding neuropsychiatric problems using self-report and significant other report interchangeably is important to be aware that the perspectives of these two informant source differ significantly.

3.3 A Profile of Neuropsychiatric Problems and Their Relationship to Quality of Life for Parkinson's Disease Patients Without Dementia

(In Press-Journal of Parkinsonism and Related Disorders. Avaliable online July 2007)

3.3.1 Abstract

A substantial number of patients with Parkinson's disease have symptoms consistent with a range of neuropsychiatric problems including, anxiety, apathy, fatigue and depression. Although a number of studies have examined individual symptoms, there is little information on the profile of neuropsychiatric symptoms that are associated with PD and their impact on quality of life. We examined the frequency of neuropsychiatric symptoms for 49 patients with PD and found that over 40% had symptoms consistent with depression, 40% with physical fatigue, 38% with mental fatigue, 38% with apathy and 32% with sleep problems. Overall, neuropsychiatric problems were common with more than 77% of the patients reporting symptoms associated with at least one problem and over 46% with 3 or more problems. Increased symptoms consistent with depression and anxiety and the presence of hallucinations also predicted poorer quality of life after controlling for motor symptoms. Given the high frequency of neuropsychiatric symptoms and their potential impact on an individuals' quality of life, increased recognition by clinicians is important so that appropriate intervention strategies may be implemented.

3.3.2 Introduction

Neuropsychiatric symptoms frequently accompany the motor problems that are characteristic of PD and are increasingly recognised as an important cause of disability even in the absence of dementia. Neuropsychiatric symptoms have been associated with reduced independence and decreased quality of life for patients with PD (Cubo et al., 2002; Weintraub & Stern, 2005), and are important predictors of caregiver distress which may result in early rest home placement. However, neuropsychiatric symptoms are often not recognized by treating physicians (Shulman, Taback, Rabinstein, & Weiner, 2002) and there is still a lack of available information regarding the typical profile associated with PD.

Neuropsychiatric symptoms often accompany disorders of the basal ganglia and in PD are thought to result partly from the degeneration of the fronto-striatal circuits (Chow & Cummings, 1999). However, other factors also contribute to their prevalence including complications of treatment therapy, the individual's reaction to having a debilitating disorder and the level of pain associated with the symptoms of PD. Varying prevalence rates have been reported for neuropsychiatric symptoms in PD patients depending on methodology, with up to 70% reported as having symptoms consistent with depression (Burn, 2002b), 40% for anxiety (Starkstein et al., 1992), 30% for hallucinations (Fenelon, Mahieux, Huon, & Ziegler, 2000), 43% for apathy (Isella et al., 2002; Starkstein et al., 1992), 40% for fatigue (Shulman, Taback, Bean, & Weiner, 2001) and 80% for sleep problems (Factor, McAlarney, Sanchez-Ramos, & Weiner, 1990; Tandberg, Larsen, & Karlsen, 1999).

Although the presence of individual non-motor symptoms has been well reported there is little information regarding a typical profile of non-motor symptoms

associated with PD without dementia. Two recent studies have described a range of symptoms using a single group of patients. Aarsland et al., (1999) examined the frequency of neuropsychiatric symptoms in a group of 139 PD patients (H&Y stage I-IV) with the Neuropsychiatric Inventory (Cummings et al., 1994) and found depression (38%) and hallucinations (27%) to be the most common disorders, with 61% of the sample reporting at least one symptom. Psychiatric symptoms were more common among patients in rest homes and those with cognitive impairment. However, 42% of their sample either met the criteria for or had questionable dementia. (Shulman, Taback, Bean, & Weiner, 2001) reported sleep disturbance (47%) and sensory symptoms (63%) as being the most common neuropsychiatric symptoms in a group of 99 PD patients (H&Y I-IV) without dementia. High rates of fatigue (40%), depression (36%) and anxiety (33%) were also reported in this group. Shulman et al. (2001) also found comorbidity to be high, with 59% of the patients having two or more symptoms and 25% having four or more.

Given the relatively high frequency of neuropsychiatric problems associated with PD, it is important to identify their impact on patients' everyday lives. Indeed, various neuropsychiatric problems have been found to contribute to the reduction in quality of life in PD patients, in addition to the motor symptoms associated with the disease (Cubo et al., 2002; Schrag, Jahanshahi, & Quinn, 2000). However, to date there has been no systematic study of the contribution that different neuropsychiatric problems make to quality of life for patients with PD.

Thus we had three goals in the present research. First, we wanted to determine the profile of neuropsychiatric symptoms in a group of PD patients without dementia and to examine comorbidity. Second, because many neuropsychiatric problems such

as apathy, fatigue, depression and sleep disturbance have a considerable degree of symptom overlap, we examined the relationships among the neuropsychiatric outcome measures. Finally, we examined the relationship between neuropsychiatric problems, motor symptoms and quality of life.

3.3.3 Statistical Analysis

The percentage of individuals with neuropsychiatric problems was calculated using previously validated cut-offs. Quantitative data are also reported in terms of means and standard deviations. Pearson correlation was employed to assess the relationships among the different neuropsychiatric problems and also between clinical /demographic characteristics and neuropsychiatric problems. Multiple regression analysis was used to assess the influence of motor impairment and neuropsychiatric problems on quality of life.

3.3.4 Methods

Approval for the study was granted by the Canterbury Ethics Committee and informed consent was obtained from patients. Patients, with a confirmed diagnosis of idiopathic PD, were invited to take part in the study through a letter from their neurologist. Inclusion criteria were as follows: no evidence of another major medical illness, no evidence of dementia (MMSE $\geq$25) and less than 80 years of age. From the 115 patients contacted, 56 patients who met the inclusion criteria (31 males and 18 females) volunteered to take part. Of these patients, two withdrew due to illness and 5 did not complete the take home tests, resulting in their exclusion. The clinical and demographic characteristics of patients included in this study are displayed in Table 20.

Table 20: Clinical and demographic characterstics of Parkinson's disease patients.

	Mean (SD)	Range
Age	66.5 (6.8)	52.0 - 77.0
MMSE[1]	28.6 (1.3)	25.0 - 30.0
PD onset[2]	6.0 (4.2)	0.3 - 23.0
UPDRS[3]	29.6 (9.7)	13.0 - 53.0
Tremor Score	0.6 (0.4)	0.0 - 1.9
Non Tremor Score	1.2 (0.4)	0.5 - 2.6
S&E[4]	81.5% (0.1)	30.0% - 100.0%
H&Y[5]	Level 1 (n=9)	Level 1.5 (n=6)
	Level 2 (n=10)	Level 2.5 (n=13)
	Level 3 (n=8)	Level 4 (n=3)

[1] Mini Mental Status Exam;[2]Number of years since onset of Parkinson's disease symptoms; [3]Unified Parkinson's Disease Rating Scale (motor score component); [4] Modified Schwab and England Activities of Daily Living Scale; [5] Hoehn & Yahr stage.

3.3.5 Procedure

This study forms part of a broader project examining the cognitive outcomes for patients with PD that was conducted over three testing sessions. Information regarding current cognitive status, motor symptoms, hallucinations, sleep problems and depression were all collected as part of the first session. Patients were also asked to take home and complete questionnaire forms which assessed symptoms of apathy, fatigue, and anxiety. Patients were specifically requested to complete the forms by themselves and not to discuss their answers with anyone else. Details regarding how to complete the forms were first explained during the first testing session and patients

were asked to return them when they attended the second session. Any questions or difficulties were addressed when the forms were returned.

Instruments used to collect clinical characteristics

1) A semi-structured interview was used to gather demographic and clinical details and included information about patient health history, drug use, age and duration of PD.

2) The Mini Mental Status Exam (MMSE) provided information regarding current cognitive functioning (Folstein, Folstein, & McHugh, 1975). A variety of cut-offs have been suggested for this instrument, but scores below 23-24/30 have been reported as having high sensitivity and specificity in identifying individuals with dementia (O'Connor et al., 1989). For this study a score of ≥ 25 was used as one of the inclusion criteria.

3) Unified Parkinson's Disease Rating Scale (UPDRS) (Fahn & Elton, 1987). Three scores were generated using this scale, a) The severity of motor symptoms was rated using the motor section; b) Tremor score (calculated as the average of items 16 and 20-26), and c) non tremor score (calculated as the average of items 5,7,12-15, 18, 19, and 27-44) (as outlined by Lewis et al., 2003).

4) The Hoehn and Yahr (H&Y) was used to rate the stage of the disease (Hoehn & Yahr, 1967). In this study the modified version of this scale was used which uses increments of 0.5 in the midranges.

5) A global measure of overall functional status was evaluated using the Modified Schwab and England Activities of Daily Living Scale (S&E), and provided a global measure of overall functioning in activities of daily living, including

ability to complete personal hygiene and daily chores without difficulty, slowness or impairment. A scale of 0-100% was used where 0% represents a vegetative state and 100% represents total independence (Ramaker, Marinus, Stiggelbout, & Van Hilten, 2002).

Instruments used to collect Neuropsychiatric information

1) Sleep Disturbance: The frequency of sleep disturbance was assessed using a single screening item contained in the UPDRS (Fahn & Elton, 1987). Patients were asked to respond with Yes/No to the question, "Do you have any problems with your sleep?"

2) Hallucinations: presence of hallucinations were assessed using the UPDRS which uses a 5 point scale where 0=None, 1=Vivid dreaming, 2= "Benign" hallucinations with insight retained, 3= Occasional to frequent hallucinations or delusions without insight, 4= Persistent hallucinations, delusions or florid psychosis (Fahn & Elton, 1987). For the purposes of this study, hallucinations were considered to be present if the patient scored greater than two.

3) Symptoms of depression were assessed using the Beck Depression Inventory (BDI-II) (Beck, Steer, & Brown, 1996). The BDI-II consists of 21 items, each rated from 0 to 3. A threshold of 14 and above is recommended for detecting the presence of depression (probable depression), and 9 and above for screening purposes (possible depression). For this study a score of ≥ 9 was taken as evidence of depression (Leentjens, Verhey, Luijckx, & Troost, 2000).

4) Anxiety was assessed using the Hospital Anxiety and Depression Scale (HADS), which consists of 14 items. Of these, seven relate to anxiety and are each rated on a four point scale (0-3) with a maximum score of 21. A threshold of 10 has been recommended for detecting probable anxiety, with

above 8 for possible anxiety. For this study score of ≥ 8 was taken as evidence of anxiety (Zigmond & Snaith, 1983).

5) Fatigue was assessed using the Fatigue Severity Scale (FSS) (Krupp, LaRocca, Muir-Nash, & Steinberg, 1989). This self-report questionnaire consists of 9 items, each scored on a 7 point scale where 1 indicates "strongly disagree" and 7 "strongly agree". For this study the questionnaire was modified so that mental fatigue and physical fatigue could be examined separately. Patients were asked to answer each item in separately in terms of mental and physical fatigue providing two scores Average scores were then calculated. A cut-off of >4, which has previously been used for patients with PD, was used for both scores to indicate presence of mental or physical fatigue (Shulman, Taback, Bean, & Weiner, 2001).

6) Apathy was assessed using the Apathy scale (Starkstein et al., 1992) which is a 14 item self-report measure. Participants are asked to indicated the extent to which each of the 14 statements applied to them over the last month using a 4 point scale: not at all, slightly, some, a lot. We used the recommended cut-off of >14 (Starkstein et al., 1992).

Measure used to evaluate Quality of Life

1) Quality of life was assessed using The Parkinson's Disease Questionnaire (PDQ-39) (Jenkinson, Fitzpatrick, & Peto, 1998). The PDQ-39 is a 39 item self-report questionnaire developed to assess the impact of PD on an individual's daily life. The questionnaire contains eight dimensions: a) Mobility (10 items); b) Activities of daily living (6 items); c) Emotional well-being (6 items); d) Stigma (4 items); e) Social support (3 items); f) Cognitions (4 items); g) Communications (3 items); h) Bodily discomfort (3 items).

Participants were asked to indicated the extent to which each of the 39 items applied to them over the last month, using one of five response categories: never, occasionally, sometimes, often, always or cannot do at all. Scale scores were then calculated from 0 (no problems at all) to 100 (maximum level of problems) using the formula supplied in the manual, which takes into account the different number of questions used in each dimension. A single index score was calculated by averaging the eight scale scores.

3.3.6 Results

Table 21 displays the mean and standard deviation for the entire sample and also percentage of patients who exceeded the cut-offs for each of the 7 neuropsychiatric outcomes. Overall, neuropsychiatric problems were extremely common with over 77% of the patient sample reaching the cut-off for one or more problems (11/49=0; 6/49=1; 9/49=2; 14/49=3; 2/49=4 and 4/49=5). Physical fatigue, mental fatigue, depression and apathy were the most frequent neuropsychiatric problems, and were reported by over 38% of the patients. Sleeping problems were reported by 32% of the patients. Anxiety and hallucinations were less frequent, with just over 16% and 12% respectively of the patients meeting the cut-off points.

Table 21: Means, standard deviations and percentages of patients with problems for each neuropsychiatric measure.

	Mean (SD) for total group	Percentage (n) with problems	Range
Physical Fatigue	3.9 (1.6)	40.1% (20/49)	1.0 - 6.9
Mental Fatigue	3.7 (1.6)	38.8% (19/49)	1.0 - 7.0
Depression	7.9 (5.0)	40.1% (20/49)	0.0 – 19.0
Anxiety[2]	5.1 (3.6)	16.7% (7/42)	0.0 – 17.0
Apathy	11.9 (5.9)	38.8% (19/49)	0.0 – 25.0
Hallucinations	N/A[1]	10.2% (5/49)	N/A[1]
Sleep Disturbance	N/A[1]	32.7% (16/49)	N/A[1]

[1]N/A = not applicable these measures used a single yes/ no format. [2] The Hospital Anxiety and Depression scale (HADS) used to detect the presence of anxiety was only completed by 42 of the 49 patients.

A major goal was to assess the relationship between the different neuropsychiatric problems because there is considerable symptom overlap. As can be seen on Table 22, there was a strong positive correlation between physical and mental fatigue. There were also significant positive relationships between physical fatigue, apathy and depression and between physical fatigue, anxiety and depression. By contrast, mental fatigue and hallucinations were only significantly correlated with depression, and there was no significant association between sleep and any of the other measures.

Table 22: Correlations between neuropsychiatric measures.

	Physical Fatigue	Mental Fatigue	Depression	Anxiety	Apathy	Hallucinations	Sleep Disturbance
Physical Fatigue	----						
Mental Fatigue	0.80***	----					
Depression	0.36*	0.30*	----				
Anxiety[1]	0.32*	0.24	0.67***	----			
Apathy	0.30*	0.28	0.40**	0.24	----		
Hallucinations	0.19	0.12	0.32*	0.29	0.18	----	
Sleep Disturbance	0.09	0.11	0.10	0.26	0.19	0.11	----

*p<0.05;**p<0.01;***p<0.001.

We also examined the association between clinical/demographic characteristics and neuropsychiatric outcomes. As can be seen from Table 23, fatigue and apathy scales and the presence of hallucinations were positively correlated with measures of motor impairment using the H&Y and tremor /non tremor scores derived from the UPDRS. Sleep problems were positively correlated with disease duration. There was no association between scores of depression and anxiety on any of the clinical or demographic characteristics and no significant association with age for any neuropsychiatric outcome.

Table 23: Correlations for clinical /demographic characteristics and neuropsychiatric problems.

	Physical Fatigue	Mental Fatigue	Hallucinations	Apathy	Sleep problems	Depression	Anxiety
Gender	-0.08	-0.22	0.04	-0.26	-0.79	-0.02	-0.15
Age	0.12	0.05	-0.05	-0.13	-0.13	-0.17	-0.05
Disease Duration[1]	0.10	0.26	-0.20	-0.07	0.37*	-0.16	0.10
H&Y[2]	0.43**	0.45**	0.49***	0.25	0.07	0.15	0.13
UPDRS[3]	0.40**	0.33*	0.30*	0.31*	-0.05	0.08	0.03
Tremor Score	0.26	0.16	-0.00	0.15	0.01	-0.06	0.07
Non Tremor score	0.42**	0.40**	0.46***	0.35*	-0.01	0.20	0.07
S&E[4]	-0.39**	-0.39**	-0.58***	-0.40**	-0.02	-0.27	-0.07

[1]Number of years since diagnosis of Parkinson's disease; [2] Hoehn & Yahr stage [3]Unified Parkinson's disease Rating Scale (motor score component); [4] Modified Schwab and England Activities of Daily Living Scale.

*p<0.05;**p<0.01;***p<0.001.

Multiple regression analyses were used to examine the influence of motor impairment and neuropsychiatric problems on quality of life (PDQ-39). Specifically, our goal was to test whether neuropsychiatric problems made an independent contribution to predicting quality of life, after controlling for the relationship between motor symptoms and quality of life. To reduce collinearity, we used a single measure of fatigue (the average of scores for mental and physical fatigue), and only the tremor and non-tremor UPDRS scores were included as measures of motor symptoms.

Scores for each PDQ-39 domain, as well as the overall score, were used as dependent variables. For each dependent variable, motor symptoms were entered on the first step, and each neuropsychiatric symptom was then entered separately on the second step. Beta weights for tremor and non-tremor scores from the first step, and for each neuropsychiatric symptom on the second step, are listed in Table 24. Also shown is the incremental variance accounted for PDQ-39 scores by the each neuropsychiatric symptom (R^2 change). Table 24 shows that non-tremor but not tremor scores were significantly related to overall quality of life (PDQ-Total). Among neuropsychiatric problems, anxiety, depression and the presence of hallucinations explained significant amount of variance after controlling for motor symptoms.

We also examined the effects of neuropsychiatric problems for each of the different quality of life domains measured by the PDQ-39. Table 24 shows that whereas non-tremor scores were significantly related to quality of life for all domains except stigma, tremor scores were not. Neuropsychiatric symptoms also explained significant variance in different aspects of quality of life. Anxiety was significantly related to quality of life, after controlling for motor symptoms, for each of the PDQ-39 domains. A similar finding was evident for depression which also accounted for significant incremental variance in quality of life scores for all domains except for perception of social support. Also presence of hallucinations accounted for significant variance in the domains of daily living, emotional well being, bodily discomfort and overall poorer quality of life.

Table 24: Beta weights for tremor, non-tremor and each neuropsychiatric symptom for regression analyses predicting Parkinson's Disease Quality of Life Questionnaire. R2 change for each symptom is shown in parentheses.

	Tremor	Non Tremor	Anxiety[1]	Apathy	Fatigue	Depression	Sleep	Hallucinations
PDQ-Total	0.06	0.61***	0.69*** (0.46)	0.22 (0.04)	0.22 (0.04)	0.51** (0.23)	0.17 (0.02)	0.39** (0.10)
Subscales								
Mobility	-0.10	0.71***	0.43** (0.18)	-0.02 (0.00)	-0.01 (0.03)	0.28* (0.07)	-0.03 (0.00)	0.20 (0.03)
Activities of Daily Living	0.14	0.60***	0.36** (0.12)	0.30* (0.08)	0.28* (0.06)	0.25* (0.06)	0.21 (0.04)	0.30* (0.07)
Emotion	0.03	0.33*	0.78** (0.60)	0.21 (0.04)	0.20 (0.03)	0.66*** (0.41)	0.13 (0.02)	0.45** (0.16)
Stigma	0.14	0.11	0.45** (0.20)	0.21 (0.04)	0.04 (0.00)	0.34* (0.11)	0.14 (0.02)	0.24 (0.05)
Social Support	0.15	0.36*	0.40** (0.16)	0.14 (0.02)	0.24 (0.05)	0.26 (0.06)	0.14 (0.02)	0.10 (0.00)
Cognitive Impairment	0.23	0.48***	0.57*** (0.32)	0.33** (0.09)	0.35** (0.09)	0.42*** (0.16)	0.03 (0.00)	0.38** (0.11)
Communication difficulties	0.07	0.49***	0.37* (0.14)	0.40** (0.14)	0.09 (0.00)	0.28* (0.08)	0.23 (0.05)	0.28 (0.06)
Bodily discomfort	0.03	0.39**	0.47** (0.22)	0.05 (0.00)	0.27 (0.06)	0.28* (0.08)	0.20 (0.04)	0.39** (0.12)

[1]Only 42 patients completed the anxiety scale.
* $p<0.05$; **$p<0.01$; *** $p<0.001$

By contrast, apathy was only significantly related to communication difficulties and the perception of cognitive impairment after controlling for motor symptoms. Both sleep difficulties and increased fatigue were only significantly associated with cognitive impairment. Overall, these results show that

neuropsychiatric problems are associated with significant variance in quality of life for PD patients after controlling for the effects of motor symptoms.

3.3.7 Discussion

The data presented here suggest that neuropsychiatric problems are common for patients with PD. Over 77% of the patients reported symptoms consistent with at least one problem and more than 46% with 3 or more problems. Over 40% of the sample had symptoms consistent with depression, 40% physical fatigue, 38% mental fatigue, 38% apathy and 32% reported having sleep problems. Symptoms consistent with anxiety were reported by 16% of the patients and the presence of hallucinations by 10%. Given the overlap between symptoms we also examined the relationship between these neuropsychiatric outcomes. There were strong positive correlations between physical and mental fatigue, and between fatigue, apathy and depression. By contrast, the presence of hallucinations was only significantly related to depression, and there was no significant correlation between sleep disturbance and any of the other measures.

In terms of the association between clinical/demographic and neuropsychiatric problems, motor impairment but not age, gender or disease duration was associated with all of the neuropsychiatric problems except for anxiety and depression. In terms of motor symptoms, non-tremor scores but not tremor scores were significantly related to neuropsychiatric problems.

We also found that in addition to motor deficits, neuropsychatric problems contributed to reduced quality of life in patients with PD. Anxiety, depression and the presence of hallucinations were significantly associated with an overall poorer quality of life, after controlling for the relationship between motor symptoms and quality of

life. When aspects of quality of life were considered separately, anxiety and non tremor scores were always predictive of lower quality of life. Similarly, depression was associated with lower quality of life for every domain apart from level of social support. By contrast, fatigue and increased sleep problems were only associated with decreased self ratings of cognitive impairment and apathy with decreased self ratings of cognitive impairment and communication difficulties.

Our results are consistent with other studies which have reported similar levels of depression, fatigue and sleep disturbance (Isella et al., 2002; Karlsen, Larsen, Tandberg, & Jorgensen, 1999; Rojo et al., 2003; Shulman, Taback, Bean, & Weiner, 2001). The prevalence of anxiety was somewhat lower here than in previous studies (Shulman, Taback, Bean, & Weiner, 2001). However, our study used the HADS while Schulman et al., (2001) used the Beck Anxiety Scale, and there is currently no information regarding the relative sensitivity of these two measures with PD patients.

Neuropsychiatric problems are increasingly recognized as contributing to poorer quality of life in patients with PD (Chapuis, Ouchchane, Metz, Gerbaud, & Durif, 2004; Cubo et al., 2002). Fortunately many of the neuropsychiatric problems associated with this group may be ameliorated with appropriate intervention. For example recent research has piloted patient education regarding information on problems associated with degenerative disease as being beneficial to patients with PD and their caregivers (Macht et al., 2007). However, identification of individuals experiencing these problems may require screening of all patients because the association between disease duration and severity (as measured by motor symptoms) is inconsistent (see Shrag, 2006 for review). Indeed, in the present study disease

duration was significantly correlated with only one of the seven neuropsychiatric problems that we examined.

It is important to acknowledge some possible limitations of our study. Although it was attempted to recruit a representative sample, only patients who volunteered were included, and thus it is possible that they were healthier than those who did not respond. Also, inclusion criteria were restricted to those patients who did not have another major health problem. Arguably, both of these factors may have reduced the representativeness of the sample. Nevertheless, these results still demonstrate that for many PD patients, neuropsychiatric problems as well as motor symptoms may contribute to reduced quality of life.

The identification of neuropsychiatric problems in patients with PD is important because these problems are amenable to intervention, and a lack of timely intervention may needlessly reduce the individuals' quality of life. Given that neuropsychiatric problems are not consistently associated with other more overt signs of the disease, such as motor impairments, all patients should routinely be screened for commonly occurring problems such as anxiety, depression, and fatigue.

3.4 Neuropsychiatric problems in Parkinson's Disease: Comparisons Between Self and Significant OtherReport

(In review Journal of Aging and Mental Disorders.)

3.4.1 Abstract

Neuropsychiatric problems occur frequently in patients with Parkinson's disease without dementia, and may cause distress for both patients and their caregivers. However, much of the relevant research has used reports from caregivers and patients interchangeably. The main aim of this study was to determine the level of agreement between significant other and patient report of neuropsychiatric problems. Forty-nine patients who met the inclusion criteria and 43 informants who knew the patient well (significant others) participated in the study. Ratings of patients' behavior by the significant others, and the stress they experienced, were obtained using the Neuropsychiatric Inventory (NPI). Information from patients was obtained using commonly-used rating scales and previously validated cut-offs. Both the patients and the significant others also completed the Frontal Systems Behavior Scale which assesses behaviors associated with apathy, disinhibition, and executive dysfunction. Although the frequencies of neuropsychiatric problems reported by significant others and the patients were similar, the level of agreement was low: 40.9% for apathy, 28% for hallucinations, 39% for depression, 25% for sleep problems and only 7.7% agreement for the presence of anxiety. Agreement between significant other and self-report was still low when both completed the same rating scale in terms of apathy ($r = 0.36$), disinhibition ($r = 0.16$) and executive dysfunction ($r = 0.00$). In addition, stress reported by significant others was associated with the perception of presence of neuropsychiatric problems in the patient, not just the presence of these problems. Overall, results show that there is a low level of agreement between significant other and self-report of neuropsychiatric problems.

3.4.2 Introduction

A significant proportion of patients with PD are reported to experience a range of neuropsychiatric problems including sleep disturbance, fatigue, depression and anxiety (Aarsland & Karlsen, 1999; Bronnick, Aarsland, & Larsen, 2005; McKinlay et al., 2007; Shulman, Taback, Bean, & Weiner, 2001). These problems have been associated with reduced quality of life for the patient, increased caregiver distress, and early rest home placement (Aarsland, Larsen, Karlsen, Lim, & Tandberg, 1999; Aarsland, Larsen, Tandberg, & Laake, 2000; Fernandez, Tabamo, David, & Friedman, 2001). Routine assessment for their presence should provide an opportunity for clinical interventions that will reduce caregiver distress and prolong independence for patients with PD. However, there is no widely-accepted assessment methodology for these neuropsychiatric problems. Moreover, self-ratings and reports from significant others have often been used interchangeably (Aarsland & Karlsen, 1999; Shulman, Taback, Bean, & Weiner, 2001) with the assumption that they are equally valid measures of the patients' symptoms. This assumption may not be correct. Thus it is important to determine whether reports from patients and significant others provide equivalent information.

The level of agreement between self versus significant-other reports of neuropsychiatric symptoms for patients with PD is yet undetermined. These two means of reporting may provide very different information about the patient's status. Whereas significant others' reports are based on their observations, the patient is describing their own symptoms based on personal experience that may or may not be accompanied by overt behaviours and which they may not have communicated with anyone else.

Even in the context of the healthy elderly, self and significant-other report may not be interchangeable. For example, McAvay et al (2004) examined the frequency of depression reported by the elderly compared to that of an informant and found that a number of elderly people who self-reported depressive symptoms were not identified by the informant and vice versa. Overall, informants tended to underestimate the presence of depression, identifying these symptoms in only 11% of individuals compared to a self-reported frequency of 18% (McAvay, Bruce, Raue, & Brown, 2004).

Both self and significant-other reports have potential problems. For example, self-report from patients with PD may be problematic because cognitive deficits that are frequently associated with this disorder may impair their ability to accurately describe problems. It is known that the agreement between significant-other and self-report decreased with more severe cognitive problems in Huntington's disease suggesting that as cognitive status becomes impaired, patient assessment is less accurate than that obtained from a caregiver (Chatterjee, Anderson, Moskowitz, Hauser, & Marder, 2005). Conversely, the reports of significant others may be influenced by their own level of distress. Mangone et al (1993) reported that the best predictor of feelings of burden for the caregivers of patients with probable Alzheimer disease was their report of perceived behaviour problems (Mangone et al., 1993).

The primary objective was to examine the level of agreement between ratings of neuropsychiatric symptoms reported by PD patients and those reported by a significant-other. Rating scales were used that are commonly found in the literature and which separately examine self or significant-other reports of neuropsychiatric symptoms in PD patients. Secondly, the relationship between the significant other's

own level of distress and his/her perception of neuropsychiatric symptoms in the patient was examined. As discrepancies in many commonly used neuropsychiatric measures could be explained by the fact that they represent different psychometric instruments and lack common measures, the Frontal Systems Behaviour Scale (FrSBe) was also used, which is completed by both the patient and their significant other. This scale provided a method to directly compare the level of agreement between the two methods of reporting.

3.4.3 Methods

Approval for the study was obtained from the Upper South B Canterbury Ethics Committee and informed consent was obtained from the patients. Patients were also asked to nominate an informant (a "significant other" who knew them well) who would provide information regarding the patients' everyday functioning and general behavior. Informed consent was obtained independently from all nominated significant others.

Participants

Patients in the Canterbury region of New Zealand with a confirmed diagnosis of idiopathic PD, identified by two experienced neurologists, were invited to take part. Inclusion criteria required no evidence of any other major medical illness, no evidence of dementia (MMSE $\geq$25), and being between 55 and 79 years of age. Of the 115 letters that were mailed out, 11/115 (9.6%) could not participate due to illness or dementia, 8/115 (9.6%) were deceased, 8/115 (6.9%) declined, 34/115 (26.9%) did not respond. A total of fifty-four patients who met the inclusion criteria volunteered to take part. Five of these patients did not complete the take home tests and were excluded. Forty-nine patients, of whom 43 were also able to provide a significant

other contact, took part in the study. In the majority of cases (approximately 90%), the significant other was a spouse. The clinical and demographic characteristics of patients who were included are listed in Table 25.

Table 25: Clinical and demographic characteristics, Parkinson's disease patients.

	Mean	Range
Age	66.6 (6.8)	52.0 - 77.0
MMSE[1]	28.5 (1.3)	25.0 - 30.0
PD Duration	6.0 (4.2)	0.3 - 23.0
UPDRS[2]	26.6 (9.7)	13.0 - 53.0

[1] Mini Mental Status Exam;[2]Parkinson's Disease Rating Scale (motor score component).

3.4.4 Procedure

Patients were assessed while on PD medication. Information regarding current cognitive status, motor symptoms, hallucinations, sleep problems and depression were all collected during the session. Patients were also asked to complete self-report forms later at home regarding symptoms of apathy, and anxiety. Details on how to complete these forms were explained during the session, and patients were asked to return these approximately seven days later. Any questions or difficulties regarding the completion of the forms were addressed at this time. Patients were specifically requested to complete the self-report forms independently, unless they required help with writing. Information regarding the patients' everyday activities and general behavior were collected during a face-to-face interview with the nominated significant other. In the majority of cases, these were conducted by a second interviewer while the patients themselves were being assessed.

Clinical and demographic characteristics

1) A semi-structured interview was used to gather demographic and clinical details including age, time since diagnosis of PD and current medications.

2) The Mini Mental Status Exam (MMSE) provided information regarding current global cognitive status, with 30 being the maximum score that may be achieved (Folstein, Folstein, & McHugh, 1975). A variety of cut offs have been suggested for this instrument, but scores below 23-24/30 have been reported as having high sensitivity and specificity in identifying individuals with dementia (O'Connor et al., 1989). In this study, patients were included if they scored ≥25.

3) The Unified Parkinson's Disease Rating Scale (UPDRS) (Fahn & Elton, 1987) motor section (section III) was used to rate current motor impairment. Scores on this scale range from 0-108, with higher scores indicating greater motor impairment.

4) The Hoehn and Yahr (H&Y) was used to rate the stage of the disease (Hoehn & Yahr, 1967). The modified version of this scale was used, which has increments of 0.5 in the midranges (stage 1, (n=9); 1.5,(n=6); 2, (n=10); stage, 2.5, (n=13); 3, (n=8); 4,(n=3)).

Neuropsychiatric information using self report only.

1) Symptoms of depression were assessed using the Beck Depression Inventory (BDI-II) (Beck, Steer, & Brown, 1996). The BDI-II consists of 21 items, each scored from 0 to 3. A threshold of 14 and above is recommended for detecting the presence of depression (probable depression), and 9 and above for screening purposes (possible depression). To be comparable with the Neuropsychiatric Inventory (NPI) which screens for both low mood

(dysphoria) and depression, we used a cutoff of ≥9 as evidence of depressive symptoms.

2) Anxiety was assessed using the Hospital Anxiety and Depression Scale (HADS), which consists of 14 items (Zigmond & Snaith, 1983). Of these, seven relate to anxiety and are each rated on a four point scale (0-3) with a maximum score of 21. A threshold of 10 has been recommended for detecting probable anxiety, with above 8 for possible anxiety. To aid comparison with the NPI, a score of ≥8 was taken as evidence of symptoms of anxiety (Zigmond & Snaith, 1983).

3) Apathy was assessed using the Apathy scale (Starkstein et al., 1992) which is a 14 item self-report measure. Participants are asked to indicated the extent to which each of the 14 statements applied to them over the last month using a 4 point scale: not at all, slightly, some, a lot. The recommended cut-off of >14 was used for this study (Starkstein et al., 1992).

4) Sleep Disturbance: The frequency of sleep disturbance was assessed using a single screening item contained in the UPDRS (Fahn & Elton, 1987). Patients were asked to respond either Yes or No to the question, "Do you have any problems with your sleep?"

5) Hallucinations: The presence of hallucinations was assessed by a single screening item from the UPDRS (Fahn & Elton, 1987). A 5 point scale was used where 0=None, 1=Vivid dreaming, 2= "Benign" hallucinations with insight retained, 3= Occasional to frequent hallucinations or delusions without insight, 4= Persistent hallucinations, delusions or florid psychosis. For the purposes of this study hallucinations were considered to be present if the patient scored two or higher on this scale.

Neuropsychiatric information from significant others only.

Patients' neuropsychiatric problems were assessed in a structured interview with the significant other using the Neuropsychiatric Inventory (NPI) (Cummings et al., 1994). The NPI covers 12 different areas of behavioral functioning: Delusions, hallucinations, agitation, dysphoria/depression, anxiety, euphoria, apathy, irritability, disinhibition, aberrant motor behavior, night-time behavior and appetite/eating change. Each question addresses changes in the person's behavior since the onset of the illness. The interviewee is first asked whether the behavioral change is present or absent. If it is absent the interviewer continues to the next domain, otherwise the interviewer asks about the frequency of the problem (1=occasionally, 2=often, 3=frequently, 4= very frequently) and severity (rated, 1=mild, 2=moderate, 3=severe) using the script provided in the manual. Scores for each domain were generated by multiplying frequency by severity (maximum score = 12). A total NPI score was generated by adding together the scores from each domain (for this study the 12 item score was used). Each domain was also scored in terms of how emotionally distressing the significant other found the behavior (0=no distress, 1=minimal, 2=mild, 3=moderate, 4=moderately severe, 5=very severe or extreme). Information regarding significant others' level of distress was also generated for each domain separately, and a total score was obtained by adding together the scores of the individual distress questions.

Neuropsychiatric information from both patients with PD and significant others.

Two versions of the The Frontal Systems Behaviour Scale (FrSBe) (Grace & Malloy, 2001) are available, one for self-report and another for the significant other to complete. This scale provided a method to directly compare the level of agreement

between the two methods of reporting. The FrSBe assesses three areas of behavioral functioning: apathy, disinhibition and executive functioning. The scale consists of 46 questions describing possible behaviors, with each question being answered using a 5 point scale (1 = almost never and 5 = almost always). Each question was answered in terms of how the patient was "at the present time". Raw scores were converted to age, gender and education adjusted T-scores (mean =50; SD=10), with higher scores indicating the presence of a greater number of problem behaviors. A score of 60 – 64 is considered borderline impairment, while >65 is considered to be clinically significant (Grace & Malloy, 2001).

3.4.5 Statistical Analysis

The percentage of individuals with neuropsychiatric problems was calculated using previously validated cut-offs as described in the methods section. Data are also reported in terms of means and standard deviations. Pearson correlation and t-tests were used to examine the relationship between significant other and self report.

3.4.6 Results

Table 26 shows the percentage of patients reported by significant others as having neuropsychiatric problems. One or more problems were reported in over 80% of the patients. Symptoms consistent with depression (42.2%) and difficulty sleeping (44.2%) were the most frequently reported problems. Symptoms of agitation, anxiety, apathy and eating problems were each reported in over 20% of the patients. Less frequently reported were symptoms of irritability, hallucinations, aberrant motor behavior, delusions and euphoria (< 12%).

Table 26: Significant others' reports from the Neuropsychiatric Inventory, of the percentage of patients with symptoms and the sub-scale scores.

	Percentage with symptom (>zero)	Mean (SD)[1] for patients with symptom (>zero)	Range
Delusions	4.4% (2/43)	8.0 (5.7)	1-12
Hallucinations	8.9% (4/43)	5.3 (5.0)	1-12
Agitation	20.9% (9/43)	2.6 (1.7)	1-6
Depression	42.2% (19/43)	2.3 (2.0)	1-8
Anxiety	23.3% (10/43)	3.0 (2.1)	1-8
Euphoria	2.3% (1/43)	1.0 (---)	----
Apathy	27.9% (12/43)	4.2 (3.6)	1-12
Disinhibition	9.3% (4/43)	3.3 (2.2)	1-6
Irritability	11.6% (5/43)	3.8 (2.3)	1-6
Aberrant Motor Behavior[2]	4.7% (2/43)	2.5 (0.7)	1-3
Difficulty Sleeping	44.2% (18/43)	6.2 (4.3)	1-12
Eating Behavior[3]	30.2% (13/43)	4.2 (3.4)	1-12
NPI total[4]	81.4% (35/43)	11.1 (12.8)	1-59

[1] Mean scores presented here are calculated in terms of frequency x severity according to standard Neuropsychiatric Inventory scoring instructions. [2] Aberrant motor behaviour refers to pacing or unusually repetitive behaviours e.g., opening closets or drawers; [3]Eating behaviour refers to change in food types preferred or appetite; [4]Total scores include night behavior and eating problems.

Table 27 displays the level of distress experienced by the significant other regarding each of the neuropsychiatric problems he/she reported as present in the patient. Not all significant others found the presence of neuropsychiatric problems distressing. Although over 80% of significant others reported at least one neuropsychiatric problem, only 48% reported finding any of these problems distressing. However, for those who did, the presence of delusions, hallucinations, disinhibition and irritability were each reported as causing moderate to severe levels of distress. By contrast, the reported presence of agitation, anxiety, apathy and difficulty sleeping, were associated with only mild to moderate distress in the significant other. Least distressing were the presence of eating problems and depression, which were reported as causing only minimal to mild distress.

Comparisons between the prevalence of neuropsychiatric problems using self (assessed using the BDI, HADS, Apathy Scale and the UPDRS) and significant-other reports (assessed using the NPI) were made for symptoms of apathy, anxiety, depression and the presence of hallucinations and sleep difficulties (see Table 28). Whereas reported frequency rates were similar for significant other and patient, the agreement between an individual patient's report and that of their significant other was not high. Indeed, there was a high of 40.9% agreement for the presence of apathy and a low of 7.7% agreement for the presence of anxiety. Further, patients reported hallucinations that were not identified by the significant other in 3/5 (60%) of cases. However, higher levels of agreement were found for depression (9/20; 45%), apathy (10/19; 53%) and sleep difficulties (9/16; 56%). But for anxiety, 6/7 (86%) of cases were identified by the patient and not by the significant other.

Table 27: The percentage of significant others reporting distress and the levels of distress associated with different symptoms they reported as present in the patient.

Distress was assessed using the Neuropsychiatric Inventory.

	Percentage reporting distress (scores > zero)	Mean (SD) for care-givers with symptoms (scores >zero)	Range
Delusions	2.3% (1/43)	5.0 (----)	---
Hallucinations	7.0% (3/43)	3.0 (2.0)	1-5
Agitation	11.6% (5/43)	2.2 (1.1)	1-3
Depression	30.2% (13/43)	1.8 (0.7)	1-3
Anxiety	14.0% (6/43)	2.0 (0.9)	1-3
Euphoria	0.0% (0/43)	---	---
Apathy	20.9% (9/43)	2.1 (1.2)	1-4
Disinhibition	2.3% (2/43)	3.0 (1.4)	2-4
Irritability	2.3 % (2/43)	3.0 (0.0)	---
Aberrant motor behavior	0.0% (0/43)	---	---
Difficulty Sleeping	23.3% (10/43)	2.6 (1.6)	1-5
Eating Behavior	11.6% (5/43)	1.5 (0.5)	1-2
Caregiver distress total[1]	48.8% (21/43)	5.9 (4.6)	1-16

[1]Total caregiver distress is the sum of the sub-scores

Table 28: Comparison between patient and significant other reports of neuropsychiatric problems.

	Frequency other report (n=43)	Frequency Self report (n=49)	Level of agreement
Hallucinations	4 (9.3%)	5 (10.2%)	2 (28.6%)
Depression	20 (46.5%)	20 (40.8%)	11 (39.3%)
Anxiety	7 (16.3%)	7 (18.9%)[1]	1 (7.7%)
Apathy	12 (27.9%)	19/49 (38.0%)	9 (40.9%)
Sleep difficulties	18 (41.9%)	16/49 (32.7%)	7 (25.0%)

[1] Only 37 patients, who also were able to volunteer a significant other, completed self ratings for anxiety.

Overall the correlations between significant other report versus self report and significant other distress versus self report were low for ratings of apathy, anxiety and sleep problems. The only significant correlations were for the presence of hallucinations and depression (Table 29). By contrast, there was a significant positive association between the report of neuropsychiatric symptoms by significant others and their distress (see Table 29).

Table 29: Correlations for significant other and self report of neuropsychiatric symptoms, significant other distress versus self report of symptoms and significant other report of neuropsychiatric symptoms and significant other distress.

	Significant other v self report	Significant other distress v self report	Significant other report v significant other distress
Apathy	0.22	0.16	**0.47****
Anxiety[1]	-0.02	0.02	**0.53*****
Hallucinations	**0.51*****	**0.50****	**0.99*****
Sleep Problems	0.09	-0.02	**0.63*****
Symptoms of Depression	**0.37***	0.28	**0.47****

[1]37 patients and their significant other completed the self ratings of anxiety, whilst correlations for all other measures are based on 43 patient and significant other pairs.

*p<0.05;**p<0.01;***p<0.001.

Ratings of sleep problems and hallucinations used a similar dichotomous scale for both self and significant-other reports. However, self reports of depression, apathy and anxiety used continuous measures with set cut offs, while significant other report relied on a yes/no answer format. Thus, it was possible that the lack of agreement between significant-other and self-report of neuropsychiatric problems was due to different measures used.

To overcome the difficulty outlined above, patients and significant others also reported on the presence of neuropsychiatric problems using a rating scale that enabled both to report symptoms in the same manner so that direct comparisons could be made. The Frontal System Behavior Rating Scale (FrSBe) includes many of the same problem behaviors as the NPI. For this analysis we included only those patients

who were able to volunteer a significant other (n=43). As shown on Table 30 even when the same rating scale was used, reported frequencies for significant other and patient differed. Further, significant-other reports of neuropsychiatric problems did not correspond well with patient self-report, with a high of 53.1% agreement for the presence of apathy and a low of 13.6% agreement for the presence of disinhibition.

Table 30: Comparison between patient and significant other reports for patients showing at least borderline impairment as rated by the Frontal System Behavior Rating Scale.

	Frequency other report	Frequency Self report	Level of agreement
Apathy	21/43 (48.8%)	28/43 (65.1%)	17/32 (53.1%)
Disinhibition	6/43 (14.0%)	19/43 (44.2%)	3/22 (13.6%)
Executive function	15/43 (34.9%)	26/43 (60.5%)	9/32 (28.1%)
Total Score	16/43 (37.2%)	27/43 (62.8%)	11/32 (34.4%)

Figure 5 shows the mean self and significant other ratings using the FrSBe. For each of the sub-scales, ratings by significant others were lower than those by patients. This difference was significant for ratings of disinhibition ($t = 2.5$, $df = 84$, $p < 0.02$), executive dysfunction ($t = 2.1$, $df = 84$, $p < 0.05$) and overall score ($t = 2.2$, $df = 84$, $p < 0.05$) but not for apathy (t=1.15, df=84, p>0.20). On average, patient ratings indicated borderline impairment in terms of the total score and for the subscales apathy and executive dysfunction, but not for disinhibition. However, significant other ratings for the patients were all in the average range (average range= T 50 +/- 10).

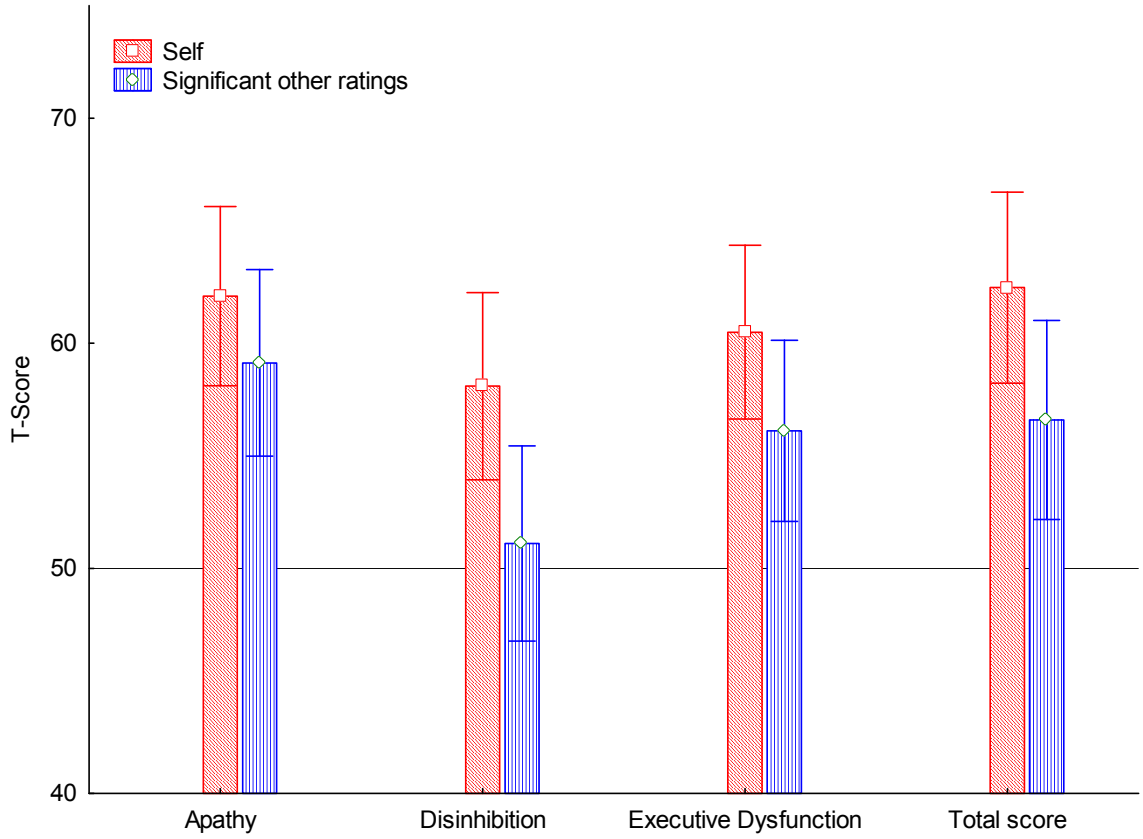


Figure 5: Comparisons between self-rating and significant other rating using the Frontal Systems Behavioral Rating Scale.
(Line indicates mean, T-score of 50 SD=10. Clinical range > 65).

The level of agreement between the two groups was also compared using Pearson correlation. The ratings of the two groups were significantly correlated ($p <$ .05) for ratings of apathy (r = .36), but not disinhibition (r = .16), executive dysfunction (r = .00) or total score (r = 0.09)

3.4.7 Discussion

This study involved a comparison of significant other and self reports for neuropsychiatric symptoms experienced by PD patients, including anxiety, depression, apathy, hallucination and sleep problems. Although similar rates of

symptoms overall were reported by patients and significant others, the level of agreement within individual dyads was low. Thus our results show that reports of significant others and patients cannot be regarded as interchangeable.

One possible reason for the lack of agreement may that significant others were asked to report on problems that could not be identified based on observable behavior, and thus relied on the patient having effectively communicated these problems to them. Moreover, the format of the measures used for ratings of self and significant other reports differed. For example, for anxiety, depression and apathy, patients were endorsing a range of symptoms and the resulting score was classified in terms of a predetermined cut-off as having or not having one of these disorders. For the significant other reports (using the NPI), all disorders were identified by a yes/no response. A yes/no format assumes that the informant has the relevant knowledge about indicative behaviors that are associated with the disorder, whereas for the patients, that knowledge is unnecessary because separate items on the scale are used for different behaviors.

It could be argued that the difference detected in this study were a result of different scales being used to assess the different neuropsychiatric problems. However, when significant others and the patient were asked to report on the symptoms using the same scale (FsSBe), the relationship between the two reports was still low for ratings of disinhibition, executive dysfunction and in terms of the overall score. The only area for which the scores between the two raters were significantly correlated was apathy. On average patients perceived themselves has having more problems than did the significant other.

Previous research with Alzheimer's patients suggests that significant others' reports can be influenced by the burden they perceive that the patients' behavior places on them (Mangone et al., 1993; Zanetti, Geroldi, Frisoni, Bianchetti, & Trabucchi, 1999). Moreover, significant other reports may have been influenced by their own mental state. Many caregivers of patients with PD are themselves depressed, and this may cause them to view the patient's behavior more negatively and endorse more neuropsychiatric symptoms (Caap-Ahlgren & Dehlin, 2002; Fernandez, Tabamo, David, & Friedman, 2001). Alternatively, patients might lack insight regarding their own behavior (Leritz, Loftis, Crucian, Friedman, & Bowers, 2004). However, neither of these explanations seems credible given that the patients tended to rate themselves as more impaired on the FrSBe than their significant other did.

In this study it was found that the number of significant others who reported particular neuropsychiatric behaviors as being distressing was much less than the number reporting the presence of these behaviors. One possible explanation for this is that caregivers reported levels of distress were influenced by their own sense of loyalty to the patient and therefore tended to under-report levels of stress. Studies of patients with dementia have reported that caregivers are reluctant to be honest regarding a patient's behavior because they did not want to upset them or they felt guilty doing so (Hughes, Hope, Reader, & Rice, 2002). Alternatively, caregivers may not report distress as a means of coping with that distress. Brandtstadter and Renner (1990) proposed that as individuals face the challenges of aging, they change their life expectations (update their goals) in an effort to preserve a sense of control. In the case of individuals who assist in the care of a patient, updating of goals may include

an acceptance that PD may result in a number of neuropsychiatric problems and not allow this to cause distress.

There were a number of limitations with this study. First, comparisons would have been enhanced had the patients and significant others reports been obtained using similar scales throughout. However, the measures we used are commonly used to assess either significant other report or self report of neuropsychiatric problems. Another potential shortcoming of the study is that we did not specifically collect information regarding the characteristics or mental state of the significant other reporters. Therefore, we could not examine differences between significant others who found the presence of a particular disorder disturbing and those who did not.

Overall, our results suggest that there may be a low level of agreement between significant other and self reports of neuropsychiatric problems. Therefore, reports from these two sources cannot be considered interchangeable. In addition, it appears that the perception of neuropsychiatric problems may influence the level of stress felt by the significant other as well as the actual presence of these problems. Many patients with PD rely on the support and assistance that is provided by a caregiver. This assistance enables the patient to remain in their own homes. However, increased caregiver stress may lead to early rest home placement at both a personal and social cost. Therefore, attention needs to be paid to the stress that caregivers experience in this role and the development of possible interventions to support them.

3.5 The Accuracy of the Unified Parkinson's Disease Rating Scale (UPDRS-Section 1) as a Screening Measure for Depression

(In Press Journal of Parkinsonism and Related Disorders. Avaliable online May 2007)

3.5.1 Abstract

The purpose of this study was to evaluate the accuracy of the UPDRS as a screening instrument for depression in Parkinson's disease (PD). Fifty nine patients with PD were screened for depression using the UPDRS. Ratings were compared with scores on the Beck Depression Inventory (BDI-II), Geriatric Depression Scale (GDS) and the Hospital Anxiety Depression Scale (HADS). A total of twenty nine patients were identified with possible depression by the BDI-II, GDS or HADS, with over one third of these (34%) assessed as having no depressive symptoms using the UPDRS. The UPDRS lacks sensitivity as a screening instrument for possible depression.

3.5.2 Introduction

Depression is a common feature in PD, with prevalence rates varying between 7-70% depending on the method of assessment and criteria and used (Burn, 2002a). Because depression can have negative effects on an individuals' cognitive functioning and quality of life, timely identification and intervention is extremely important. However, depression is often not recognized or is misdiagnosed by clinicians during routine assessment (Shulman, Taback, Rabinstein, & Weiner, 2002). To assist in the recognition of non-motor symptoms such as depression, clinicians are often guided by standardized instruments such as the UPDRS (Fahn & Elton, 1987). The UPDRS provides a comprehensive means of evaluating impairments associated with PD, and Section 1 of the assessment battery includes a question relating to the presence of depression. Although the UPDRS lacks sufficient information for use as a diagnostic tool, it is commonly used as an initial screen. Unfortunately, there is currently no information regarding the accuracy of the UPDRS as a screening tool for depression, and no guidelines for when a clinician should initiate a more detailed assessment.

This study sought to assess whether the question in the UPDRS would accurately identify patients who required further screening by using the UPDRS in addition to three depression measures that have been validated for use in the PD population: the BDI-II, GDS and HADS (Ertan, Ertan, Kizilatan, & Uygucgil, 2005; Leentjens, Verhey, Luijckx, & Troost, 2000; Weintraub, Oehlberg, Katz, & Stern, 2006). The level of agreement among these scales was examined, using the optimal suggested cut-offs for this patient group.

3.5.3 Methods

Approval for the study was obtained through the local ethics committee and patients were invited to take part through a letter from their neurologist. From the 115 patients contacted, 59 patients without evidence of dementia volunteered to take part. There were 40 males (67.8%) and 19 females (32.2%), with an average age of 66.7 years (± 7.3) (age range 48 to 79 years old) and a mean UPDRS-subscale III score of 31.0 ± 10.7. All participants were administered the GDS, BDI-II, UPDRS and the Mini Mental Status Exam (MMSE, patients were included if they scored ≥25) (Folstein, Folstein, & McHugh, 1975). A portion of the patients also completed the HADS. The GDS is a 30 item self-rated depression measure with each item answered yes/no and rated 1/0. The BDI-II consists of 21 items; each question is rated 0 to 3. Both the BDI-II and the GDS have been validated for use with PD patients, each with a threshold of 14 and above being recommended for detecting the presence of depression (probable depression), and 9 and above for screening purposes (possible depression) (Ertan, Ertan, Kizilatan, & Uygucgil, 2005; Weintraub, Oehlberg, Katz, & Stern, 2006).

The HADS consists of 14 items. Of these, seven relate to depression and are each rated on a four point scale (0-3) with a maximum score of 21. A threshold of 10 has been recommended for detecting probable depression, with above 8 for possible depression (Ertan, Ertan, Kizilatan, & Uygucgil, 2005; Weintraub, Oehlberg, Katz, & Stern, 2006; Zigmond & Snaith, 1983). For each of these self report measures, higher scores are indicative of more depressive symptoms.

The UPDRS has a single screening item for depression. A score of zero indicates no symptoms, 1= periods of sadness or guilt greater than normal, but never

sustained for days or weeks, 2= sustained depression (one week or more), 3= sustained depression with vegetative symptoms (insomnia, anorexia, weight loss, loss of interest), 4= sustained depression with vegetative symptoms and suicidal thoughts or intent. Patients with a score of 0 were considered to have no depressive symptoms, 1-2 possible, and 3-4 probable depression.

3.5.4 Statistical Analysis

Pearson correlation was employed to assess the relationship between the different measures of depression. We then examined how well the UPDRS predicted possible and probable depression, as defined by the BDI-II, GDS or HADS score exceeding the respective cut-off, through percentage agreement and Receiver Operating Characteristic (ROC) analyses.

3.5.5 Results

Significant positive correlations were obtained between all measures of depression. Correlations were moderately strong between the UPDRS and BDI-II, r = .61, $p < .001$, GDS, r = .63, $p < .001$, and HADS, r = .42, $p < .01$. The BDI-II and GDS were highly correlated, r = .77, $p < .001$, while the correlations between the HADS and BDI-II and GDS were also positive, r = .53, $p < .001$ and r = .66, $p < 001$.

Table 31 shows cross tabulations between the UPDRS as diagnostic screen and those produced by applying the appropriate cut-offs for possible and probable depression for the BDI-II, GDS, and HADS. Despite the positive correlation between the UPDRS and the three measures of depression, the UPDRS diagnostic screen agreed with the BDI-II in only 54.3% of total cases, and with the GDS and HADS in 55.9 % and 56.5% of cases, respectively. False negatives were unacceptably high: Of

the patients that had possible or probable depression according to the BDI-II and GDS, the UPDRS indicated no depression for 33% and 30% of cases, respectively. The proportion of cases identified by the HADS with possible or probable depression was significantly lower compared to the BDI, $\chi^2 = 20.54$, $df = 1$, $p < 0.001$, and the GDS, $\chi^2 = 9.14$, $df = 1$, $p < 0.01$). Patients who completed the HADS did not differ significantly from those who did not, in terms of demographic variables or levels of depression on the other three scales used.

A series of ROC analyses were conducted in which the UPDRS was used to predict possible/probable and probable depression, as defined by meeting the criteria for possible or probable depression on the BDI-II and GDS. The HADS was not used as a criterion for this analysis because it identified only a small number of cases with possible and probable depression. For sake of comparison, we also used the BDI-II and GDS to predict possible/probable depression according to the GDS and BDI-II respectively.

The UPDRS achieved only moderate levels of accuracy in predicting possible depression: AUC values for possible depression according to the BDI-II and GDS were .69 and .71, respectively. Corresponding AUC values for the BDI-II predicting possible depression according to the GDS, and vice versa, were .85 and .84, which were significantly greater than UPDRS accuracy, $z = -2.35$, $p < .01$ and $z = -1.64$, $p < .05$ (Hanley & McNeil, 1983). The UPDRS was more accurate in predicting probable depression according to the BDI-II and GDS, with AUC values of .85 and .85. These values were less than those for the BDI-II and GDS predicting probable depression according to the GDS and BDI-II, AUC's = .95 and .96, although the differences did not reach significance, $z = -1.51$ and $z = -1.52$, both *ns*.

Table 31: Cross tabulation of diagnostic screen classifications ("Not Depressed, "Possible Depression", and "Probable Depression") obtained with UPDRS and with three validated psychometric tests for depression (BDI-II, GDS, and HADS).

Category Percentage indicates the proportion of cases in each diagnostic classification for the BDI-II, GDS, and HADS. The percentage agreement column shows the percent of cases with a particular diagnostic classification for which the UPDRS gave the same classification; numbers in boldface indicate the overall percent agreement of UPDRS screen for each of the psychometric tests.

	UPDRS=0 Not Depressed	**UPDRS=1-2 Possible Depression**	**UPDRS=3-4 Probable Depression**	**Category Percentage**	**Percentage Agreement**
BDI-II [1]					
Not depressed (<9)	22	13	0	59.3	62.9
Possible (9-13)	7	6	0	22.0	46.2
Probable (≥14)	1	6	4	18.6	36.4
% UPDRS Categories	50.8	45.8	6.8		
Total Agreement					**54.3**
GDS [2]					
Not Depressed (<9)	24	15	0	66.1	61.5
Possible (9-13)	5	5	0	16.9	50.0
Probable (≥14)	1	5	4	16.9	
% UPDRS Categories	50.8	42.4	6.8		
Total Agreement					**55.4**
HADS [3]					
Not Depressed (<8)	24	17	2	93.5	55.8
Possible (8- 9)	0	2	0	4.3	100.0
Probable (≥ 10)	0	1	0	2.3	0.0
% UPDRS Categories	52.2	43.5	4.3		
Total Agreement					**56.5**

[1]Beck Depression Inventory-II; [2] Geriatric Depression Scale; [3]Hospital Anxiety Depression Scale. Only a portion of the participants completed the HADS (n=46/59).

Overall 29 of the 59 patients (49%) had scores indicative of possible depression using the BDI-II, GDS or HADS. There was no significant difference between patients who met the criterion for possible depression and those who did not in terms of years of education ($t = 0.40$, $df = 57$, $p > 0.65$), age ($t = 1.60$, $df = 57$, p

>0.10), gender (t = -0.17, df = 57, p > 0.85) or disease duration (t = -0.18, df = 57 p > 0.85).

3.5.6 Discussion

Although the UPDRS has been suggested as a suitable screen for depression in PD patients, there are no guidelines to indicate who should be referred for a more detailed assessment. This study sought to evaluate the accuracy of the UPDRS as a screening instrument for depression. Ratings on the UPDRS were compared to scores using three measures of depression validated for use with PD patients. Overall, 29 of 59 cases were identified as having possible depression by the BDI-II, GDS or HADS. The UPDRS failed to identify 34% of these cases as having any depressive symptoms whatsoever, which is an unacceptably high Type II error rate. ROC analyses showed that the UPDRS had only moderate accuracy overall for predicting possible depression, as measured by BDI-II and GDS, with average AUC = .70.

Apparently, individuals with milder symptoms were more likely to endorse "no depression" using the UPDRS. This may result from how the question is currently structured with 0 being indicative of "not present,' while a score of 1 refers to periods of sadness "greater than normal". Faced with this decision, individuals with mild symptoms may be more inclined to endorse no problems. These issues have been recognized by the UPDRS task force who are currently revising the scale with the intention making it suitable for capturing mild impairments, and who also intend to provide more detailed guidelines for clinicians (Romano, 2005).

Although there are notable differences in the structure of the BDI-II and GDS, overall there was a high level of agreement between the two measures. By contrast the HADS identified significantly fewer of the patients as having possible or probable

depression compared to the BDI-II or the GDS. It is possible that the traditional cut-off scores for this measure are too conservative for use with PD patients.

Conclusion

Because a high level of sensitivity is desirable, the UPDRS in its present form has limited utility as a screening instrument for possible depression. The routine administration of more comprehensive measures such as the BDI-II or GDS to screen for depression is therefore advisable. Cut-off scores for the HADS may need to be revised for use with PD patients.

Chapter 4 - The Cognitive Profile of Patients with Parkinson's disease

Abbreviations in test chapter 4

1) **AD** = Alzheimer's disease; 2) **ANCOVAs** = Analyses of covariance; 3) **ANOVA** = analysis of variance; 4) **BADS** = Behavioral Assessment of the Dysexecutive Syndrome; 5) **BDI-II** = Beck Depression Inventory; 6) **CANTAB** = Cambridge Neuropsychological Test Automated Battery; 7) **D-KEFS** = Delis Kaplan Executive Function System; 8) **DRS-II** = Dementia Rating Scale-II; 9) **DSM-IV** = Diagnostic and Statistical Manual Fourth Edition; 10) **FAQ** = Functional Activities Questionnaire; 11) **H&Y =** Hoehn and Yahr Staging Scale; 12) **ID/ED** = Inter Dimensional/Extra Dimensional Shift; 13) **JOL** = Judgement of Line Orientation test; 14) **MCI** = Mild Cognitive Impairment; 15) **MMSE =** Mini Mental Status Exam; 16) **NART** = National Adult Reading test; 17) **PD** = Parkinson's disease; 18) P**PD** = Parkinson's disease; 19) **PD-MCI** = Parkinson's disease with Mild Cognitive Impairment; 20) **PD-NCI** = Parkinson's disease No/minimal impairment; 21) **PD-UCI** = Parkinson's disease with Uncertain Impairment; 22) **ROF** = Rey-Osterrieth Complex Figure Test; 23) **SOC's** = Stockings of Cambridge; 24) **S&E =** Modified Schwab and England Activities of Daily Living Scale; 25) **TOL** = Tower of London; 26) **UPDRS** = Unified Parkinson's disease Rating Scale; 27) **WASI =** Wechsler Abbreviated Scale of Intelligence; 28) **WAIS-III** = Wechsler Adult Intelligence Scale 3rd edition; 29) **WMS-III** = Wechsler Memory Scale-3rd Edition.

4.1 Overview

Cognitive deficits are a feature of PD, even in the absence of dementia. A review of the existing literature indicates that deficits in the domains of memory, learning, visuoperception/visuospatial functioning, speed of mental processing and executive functions (including planning, working memory, verbal fluency, attention and set-shifting) are the most commonly affected domains of cognition that are associated with PD (see Pillon, Boller, Levy, & Dubois, 2001 for review). However, there is still considerable controversy regarding the exact profile of cognitive deficits that are associated with this disorder. It has been suggested that the lack of consensus is due to the heterogeneity of cognitive performance in PD patients that is unrelated to motor symptoms or disease duration (Lewis et al., 2003; Lewis et al., 2005). This suggestion has led to a greater focus on identifying different sub-groups of patients based on their cognitive status (Lewis et al., 2005). The identification of sub-groups of PD patients based on cognitive characteristics may be of some importance as particular groups could be at greater risk of cognitive decline and later dementia. Cognitive decline and dementia in PD have serious implications for the patient resulting in reduced quality of life, increased caregiver distress and resultant premature rest home placement (Schrag, Jahanshahi, & Quinn, 2000).

4.1.1 Difficulty with research in this area

Much of the inconsistency in results regarding cognitive deficits in PD has resulted from the application of different methodologies, diverse patient groups, heterogeneity of tasks employed and the varying levels of complexity and processing demands of the different tasks. Assessing cognitive deficits in PD poses a number of difficulties in addition to those outlined in section 1.6.2. For example, test selection is

constrained by the physical limitations of the patients. There are few cognitive test batteries that have been developed specifically for individuals with physical limitations. Further, any testing must be arranged in order to accommodate changes in physical functioning that can occur in a single session, e.g., fatigue, changes in medication effectiveness, and lack of motivation. Another important consideration is the neuropsychiatric issues that frequently accompany PD. Neuropsychiatric issues also raise the consideration of which patients to include or exclude while retaining the maximum generalisability of any data obtained.

4.2 Current Research

For this study a wide variety of tests were selected that would cover different aspects of cognition. The purpose of this extensive testing was threefold. Firstly, to identify the range and extent of cognitive problems in patients with PD compared to normal elderly. Secondly, to use this information to develop a discrete set of tests capable of identifying which patients are experiencing cognitive impairments of sufficient severity to interfere with their daily lives. Thirdly, to identify different sub-groups of PD patients based on their cognitive performance. Identification of sub-groups may enhance our understanding of cognitive impairments in PD, and also might reveal patients who are at a stage of pre-clinical dementia or mild cognitive impairment. The term mild cognitive impairment (MCI) has been used in research on Alzheimer's disease to describe a stage of cognitive decline that is greater than that associated with normal aging. Normal elderly who progress to a stage of mild cognitive impairment have been found to be more likely to develop AD. It seems likely that a stage of MCI will also be identifiable for patients with PD (PD-MCI). The identification of cognitive test that signal PD-MCI presents an opportunity to

intervene and delay the onset of more severe cognitive problems that may result in PD with dementia (PDD). This aspect of the research addresses objectives one to four briefly listed below (see section 1.14 for a full outline of the objectives for the thesis).

1. Develop a cognitive and behavioural profile for PD compared to healthy elderly.
2. To identify functional deficits that may be associated with PD.
3. To identify sub-groups of patients based on their cognitive status.
4. To develop a discrete group of non-invasive tests that will have clinical application.
5. Follow-up study to examine the stability of the cognitive groupings that emerge from the initial main study.

4.2.1 Manuscript 1 – Executive Function

To partially address objective one, the first manuscript in this chapter provides a comprehensive assessment of cognitive characteristics in patients with PD without dementia, with particular emphasis on tests that were sensitive to executive dysfunction and its sub-components. While deficits in executive functions in PD have frequently been reported, there is little information regarding which aspects are impaired or spared. In this study we found evidence of impaired performance across different aspects of executive functioning and visuospatial functioning. Notably, some aspects of executive function were intact which may provide a focus for intervention strategies for those patients with cognitive impairments. There was no evidence of deficits in the domains of memory/learning, or for measures of attention or planning. For this manuscript we assessed a single group of patients on tests that

covered a broad range of cognitive domains in order to identify a cognitive profile for PD patients.

As a caveat to this first manuscript, it is important to be aware that a selected group of PD patients were tested. Patients were excluded based on a number of criteria (as outlined in 2.2.1 of this thesis). It could be argued that all PD patients could have been included and unwanted clinical characteristics could have been entered into subsequent analyses as covariates. This approach could have improved the generalisability of the study. However, after consideration of the number of medical issues that were likely to be present in an older population, and the impact that these might have on any cognitive outcomes, the exclusion criteria adopted here were considered to be most appropriate. Another issue relates to the number of comparisons that were run between the two groups and the decision regarding statistical significance. While some statisticians suggest that Bonferroni adjustments are appropriate when multiple tests are run in order to reduce the chance of a type one error, it was determined that the resultant increase in type two errors would be unacceptable. As a compromise, the alpha level was set to $p<0.01$ and provided a full description of what was done to allow the reader to reach their own conclusion as suggested by Perneger (1998).

4.2.2 Manuscript 2 – Mild Cognitive Impairment

To address objectives two, three and four, outlined above, the second manuscript in this chapter used a data-driven method to identify sub-groups of PD patients that differed in terms of their cognitive functioning. As a related aim, this manuscript also examined whether these sub-groups differed in terms of performance in activities of daily living. Finally, from a practical point of view, it was intended to

identify, from the vast array of possibilities, a discrete set of tests that could be easily used by clinicians to determine which patients were experiencing cognitive problems that were likely to impact on their daily lives. It was hypothesised that a specific subset of tests could be identified that would be most indicative of patients with PD with Mild Cognitive Impairment (PD-MCI). Currently there is little research that has examined the range of cognitive deficits possible in PD patients or the impact that these deficits may have on daily functioning. Further, much of the research to date has addressed the heterogeneity of cognitive problems by grouping patients based on their motor symptoms, age or disease duration.

In this study three sub-groups were identified that formed a continuum of cognitive impairment from mild to severe. Compared to controls, one group had little or no cognitive impairment (PD-NCI). A second group showed a more variable pattern of mild –severe impairments (PD-UCI), while a third group had evidence of severe cognitive impairments across most of the cognitive domains tested (PD-MCI). The latter two groups were also significantly different from the control group in terms of their ability to carry out functional activities of everyday living. The severity of cognitive deficits was not associated with other clinical and demographic characteristics (e.g. age, motor impairments or disease duration). It was hypothesised that the third group represented patients who were more likely to develop frank dementia. The organisation of PD patients based on cognitive characteristics can improve our understanding of PD and appropriate interventions can be better organised to meet their specific needs.

It is important to be aware that statistical methods such as cluster analysis have associated advantages and disadvantages. Cluster analysis are useful in

revealing hidden patterns in the larger data sets (Peck, 2005). This is particularly true in the case where the population in question is heterogeneous. The hierarchical clustering (k-means clustering) procedure used in this study assigns individuals into sub-groups to maximise homogeneity within groups and heterogeneity between groups (Peck, 2005). However, there are also number possible problems with cluster analysis. Firstly, the cluster analysis will produce as many clusters as requested (Cherry, 1993). Further, as Cherry (1993) points out, it is difficult to know how many clusters exist in a given population. Moreover, cluster solutions may lack stability and change depending on the variables entered into the analysis. To address this issue, solutions were generated using 26 variables and 13 variables to test the stability of the resulting groups.

4.2.3 Manuscript 3 – Pre-clinical Dementia

The third manuscript in this chapter examined outcomes for the sub-groups one year after their initial assessment and addressed objectives four and five. The aim of the follow-up study was to examine the performance of the three sub-groups identified in manuscript two using the tests that had been found to be sensitive to cognitive impairment in PD. The groups at time two were also compared in relation to their performance at time one, it was expected that a trend for decline would be seen in the PD groups. The results indicated that, consistent with their time one performance, the PD groups performed more poorly than controls on the domains of executive functions, problem solving, and working memory and visuospatial ability, with the greatest deficits being evident for the PD-MCI group. There was no evidence of decline in cognitive functioning for any of the sub-groups between time

one and time two. However, increased cognitive problems were associated with decreased functioning in activities of daily living.

There were a number of issues that are pertinent to consider in relation to these findings. While it appears that the PD patients were consistently impaired on the domains outlined above, to confirm that these deficits represent a cognitive profile for PD patients would require testing of an independent group of PD patients. This would also enable the validity of the three clusters suggested here to be tested. No trend for decline over time was found. However, not all the patients were available for testing at time two. Some of the original group of patients had either died or were hospitalised at the time of testing and too unwell to participate. The majority of the patients that were unable to be tested at time two had been from the PD-MCI group and it is possible that the attrition of these patients influenced these results.

4.2.4 Summary

Overall we found evidence for a variety of cognitive deficits for PD patients. This finding was consistent with other research in this area. These data also added to the literature in a number of ways. The cognitive profile of patients without dementia using a broad range of domains and tests was defined. In addition, different subgroups of patients were identified based on their cognitive performance. Moreover this study extended the research in this area by examining how these problems impacted on the quality of live for individuals with PD.

4.3 Characteristics of Executive Function Impairment in Parkinson's Disease Patients Without Dementia

(In review: Journal of Neurology, Neurosurgery and Psychiatry)

4.3.1 Abstract

Executive function impairments in PD are well documented. However, information regarding the different aspects of executive functions that are impaired or spared is limited. The goal of this study was to provide a comprehensive assessment of cognitive characteristics in patients with PD without dementia, with a particular emphasis on tests that are sensitive to executive dysfunction and its subcomponents. The relationship between different cognitive domains was also examined. Forty Parkinson's patients without dementia met the criteria for this study. Each patient was individually matched in terms of age, sex and pre-morbid intelligence, to a healthy control. Outcomes for patients were compared to controls using a comprehensive set of general executive function/attention tests, and measures for subcomponents of executive function including working memory, planning, and problem solving. We also included measures of memory/learning and visuospatial skills to examine the relationship between aspects of executive function and other areas of cognition. Patients with PD showed deficits on measures of executive function, working memory, problem solving, and visuospatial skills. However, they were unimpaired on measures of planning, attention and memory/learning. Deficits in problem solving were only evident for tasks with a high visuospatial content and were no longer significant when visuospatial skills were controlled for. Overall, deficits in executive function, its subcomponents and visuospatial skills were apparent for PD patients compared to healthy controls. However, some aspects of executive function were intact, which may provide a focus for intervention strategies for those patients with cognitive impairment.

4.3.2 Introduction

It is well known that cognitive deficits are associated with Parkinson's disease (PD), and are an important cause of functional impairment in many cases, with about 30% of patients progressing to dementia (Aarsland, Zaccai, & Brayne, 2005). Cognitive deficits are associated with caregiver distress and premature rest home placement, and are therefore important in terms of both personal and social cost (Aarsland, Larsen, Tandberg, & Laake, 2000; Schrag, Jahanshahi, & Quinn, 2000). Given the relative importance of cognitive impairments, there has been considerable interest in identifying a specific cognitive profile for patients with PD to inform appropriate intervention strategies.

Neuropathological changes associated with PD are focused on the basal ganglia and thalamocortical circuits, compromising the integrity of the prefrontal lobe which is considered to play a pre-eminent role in "higher order" or executive function (Duffy & Campbell, 1994; Fuster, 2000). Executive function involves the ability to plan, initiate and monitor goal directed behaviour with the flexibility to update goals in the face of new information (Elliot, 2003). Deficits in decision making, planning, initiation, working memory, self monitoring, problem solving and inhibition are all considered to reflect executive dysfunction (Salthouse, 2005).

Given the neuropathology of PD, it has been suggested that the magnitude of cognitive deficit will reflect the degree to which the task relies on the integrity of the frontal lobe (Higginson et al., 2003; Taylor & Saint-Cyr, 1995). Moreover, deficits observed with any tasks that do not rely predominantly on the frontal lobe, such as memory and visuospatial deficits, should be secondary and related to the higher

cognitive demands that are mediated by the frontal lobes (Bondi, Kaszniak, Bayles, & Vance, 1993a).

There is an abundance of research that supports the presence of deficits in executive functioning in PD (Dimitrov, Grafman, Soares, & Clark, 1999; Farina et al., 2000; Muslimovic, Post, Speelman, & Schmand, 2005; Tamaru, 1997). However, there is considerable uncertainty regarding the different dimensions of executive functioning that might be impaired or spared for PD patients, and the degree to which these impairments affect other cognitive functions (Weintraub & Stern, 2005). Two recent publications have investigated the dimensions of executive function deficits in PD. Uekermann et al., (Uekermann et al., 2004) examined the subcomponents of executive functions impaired in early stages of PD using a group of 20 patients and reported deficits in initiation, reasoning and planning. Weintraub et al., (2005) identified planning and inhibitory control as two factors that were impaired in a group of 46 PD patients with mild to moderate symptoms. Planning was associated with decreased motivation and inhibitory control deficits with motor slowing (Weintraub et al, 2005). However, neither of these studies examined the relationship between the different subcomponents of executive function and other areas of cognitive functioning.

There were three primary objectives in the present study. First, to identify a pattern of deficits in executive function subcomponents and general cognitive deficits in PD patients without dementia, using a comprehensive set of commonly used neuropsychological tests. These tests were specifically selected based on research that has found them to be sensitive to cognitive impairment in patients with PD, and

with the potential to be used by clinicians. The second objective was to assess the relationship between cognitive deficits and the demographic and clinical features of the patient group. Finally, it was planned to examine the relationship between different domains of executive function and other areas of more general cognitive function.

4.3.3 Methods

Approval for this study was granted by the Canterbury Ethics Committee and informed consent was obtained from patients. Patients with a diagnosis of idiopathic PD confirmed by a specialist neurologist were invited to take part in the study.

Participants

Parkinson's disease group

Parkinson's patients in the Canterbury region, who could be identified at the time of this study and had not been diagnosed with dementia, were invited by letter to participate. Inclusion/exclusion criteria were as follows:

Inclusion Criteria: 1) Assessed at the Hoehn & Yahr stage I-IV; 2) Aged between 50 and 80 years; 3) Adequate or corrected hearing and vision (self report checked by examiner); 4) Stable on PD medication; 5) English as the primary spoken language. Exclusion criteria were: 1) Currently involved in a therapeutic trial; 2) History of: a) moderate or severe head injury; b) stroke or other neurological impairment; c) major medical illness; d)significant psychiatric illness requiring hospitalisation; e) suspicion of dementia symptoms (MMSE <25, DRS-II and DSM-IV criteria); f) diagnosis of, or special education for, a learning disability; g) major

depressive episode in the previous 6 months; 3) Pre-morbid IQ estimated at <85 using National Adult Reading Test (NART); 4) Currently taking medications known to have a significant effect on Central Nervous system (other than medications prescribed for the control of PD symptoms); 5) Beck Depression Inventory –II score of >17.

Of the 115 letters that were mailed, 6/115 (5.2%) of individuals with PD could not participate due to illness, 6/115 (5.2%) were deceased, 8/115 (6.9%) declined, 34/115 (29.6%) did not respond, and 21/115 (18.3%) did not meet the inclusion/exclusion criteria. After exclusions, 40 participants with PD were included in the analyses. All patients were on antiparkinsonian medication and were tested while on optimal levels of medication.

Controls

Controls were recruited from a number of sources including a previously established data base, advertisements at local clubs (bowling, hiking and table tennis) and businesses. All controls were given a brief outline of the study on first phone contact. If they were still willing to participate they were then sent an information sheet. In addition to adequate or corrected hearing and vision (self report, checked by the examiner) and being aged between 50 to 80 years of age, the same exclusion criteria listed above also applied to the control group.

4.3.4 Procedure

Assessments were carried out at the University of Canterbury over three testing sessions, each of three hours in duration. Tests were presented in a fixed order with breaks taken as required. Written consent was obtained from all participants at

the start of the first testing session after the study had been explained. All patients with PD were tested while on optimal levels of medication.

Background measures

Prior to participating in the full cognitive assessment, all patients were assessed in terms of current and pre-morbid cognitive and mental status. Additional information pertinent to the inclusion/exclusion criteria was elicited from all participants using a semi-structured interview. PD patients also underwent a clinical assessment that included the Hoehn & Yahr staging and the Unified Parkinson's Disease Rating scale to assess motor impairment.

1) National Adult Reading Test (NART) was used to estimate pre-morbid IQ. This test comprised a list of 50 "irregular" words printed in order of increasing difficulty. Words are scored 0 for incorrect and 1 for correct pronunciation (Lezak, 1995).

2) Beck Depression Inventory-II (BDI-II) consists of 21 items; each question is rated 0-3 with higher scores indicating greater intensity of symptoms (Beck, Steer, & Brown, 1996). The BDI-II has been validated for use with PD patients, with a cut off of 17 being recommended for detecting the presence of depression (Leentjens, 2004).

3) The Mini Mental Status Exam (MMSE) provided information regarding current cognitive status. Patients and healthy controls were included if they scored ≥25 (Folstein, Folstein, & McHugh, 1975).

Three additional measures were used for patients with PD to provide information regarding motor impairment and global functioning in activities of daily living.

4) Unified Parkinson's Disease Rating Scale (UPDRS) (Fahn & Elton, 1987). Three scores were generated using this scale: a) The severity of motor symptoms was rated using the motor section; b) a tremor score calculated as the average of items 16 and 20-26 on the UPDRS; and c) a non tremor score calculated as the average of items 5,7,12-15, 18, 19, and 27-44 and divided by 26 (as outlined by Lewis, Dove, Robbins, Barker, & Owen, 2003).

5) The Hoehn and Yahr (H&Y) was used to rate the stage of the disease (Hoehn & Yahr, 1967). The modified version of this scale was used with increments of 0.5 in the midranges.

6) The Modified Schwab and England Activities of Daily Living Scale (S&E), was used to provide a measure of overall functioning in activities of daily living, including ability to complete personal hygiene and daily chores without difficulty, slowness or impairment. A scale of 0-100% was used where 0% represents a vegetative state and 100% represents total independence (Ramaker, Marinus, Stiggelbout, & Van Hilten, 2002).

Neuropsychological assessment

Neuropsychological assessment covered six cognitive domains: 1) General executive function/planning; 2) problem solving; 3) working memory/attention; 4) speed of processing; 5) memory/learning; 6) visuospatial ability. Planning, problem

solving, and working memory are considered to be subcomponents of executive function, and were measured separately to provide an opportunity to examine the different aspects of executive function that might be impaired (Salthouse, 2005). Also included were measures of attention and speed of processing. Although not generally considered subcomponents of executive function, the integrity of these processes is directly linked with efficient processing of executive and general cognitive tasks.

All tests were commonly used neuropsychological measures and scored according to standard procedures. The majority of the measures used were from standardised batteries including the Wechsler Abbreviated Scale of Intelligence (WASI) [Mean 50, Standard deviation 10] (Wechsler, 1999), Delis Kaplan Executive Function System (D-KEFS)(Delis, Kaplan, & Kramer, 2001), and the Wechsler Memory Scale-III (WMS-III)(Wechsler, 1997) [both mean 10, standard deviation, 3] with age-adjusted norms. Such norms were not available for tests from the Behavioural Assessment of the Dysexecutive Syndrome (BADS) [scores range from 0-4] (Wilson, Alderman, Burgess, Emslie, & Evan, 1996), Cambridge Neuropsycholgical Test Automated Battery (CANTAB), Reading Span task, and tests of visuospatial functioning. However, all patients were individually matched for age.

Executive function/planning skills were evaluated using the following tests from the D-KEFS: Verbal Fluency test (with subtests for letter fluency, category fluency and category fluency switching) and Color-Word Interference test (with sub-tests for Inhibition and Inhibition switching). Also included in this domain were the Key Search and Zoo map from the BADS, the Intradimensional/Extradimensional Shift (ID/ED) from the CANTAB (number of stages completed, scores vary from 0-9)

and the CLOX-I (Royall, Cordes, & Polk, 1998). The CLOX is an unstructured drawing test that has two parts; for both parts of the test a maximum score of 15 is possible indicating perfect performance. In part one the participant is given the following instruction "Draw me a clock that says 1.45. Set the hands on the face so a child could read them" (Royall, Cordes, & Polk, 1998). Drawings are rated according to CLOX-1 directions.

Problem solving was assessed using the Card Sorting subtests of free sorting and sorting recognition, and the Tower Task (number of towers completed in the minimum number of moves, maximum score possible 9). Both of these tests were from the D-KEFS. Problem solving was also assessed using the Matrix Reasoning subtest from the WASI the and the Stockings of Cambridge (SOC's) from the CANTAB (number of towers completed in the minimum number of moves, maximum score possible 12), which is considered to be conceptually similar to D-KEFS Tower task.

Working memory/ attention was assessed using Letter Number Sequencing, and Digits Forward and Backward, from the WMS-III, Spatial Span (maximum sequences correctly recalled 0-9) from the CANTAB and the Daneman and Carpenter Reading Span test (scores range from 1-6).

Speed of processing was evaluated using Word Naming and Color Naming from the D-KEFS Color-Word interference test.

Memory/learning was assessed using the WMS-III, Paired Associates (immediate and delayed), Logical Memory (immediate and delayed) and the Auditory

Recall Index. The Rey Osterrieth Figure (ROF) recall after 3 and 30 minutes was also used as a measure of memory ability. All three parts of the ROF are rated the same and can vary from 0-36, with higher scores indicating more accurate performance (Spreen & Strauss, 1998).

Visuospatial/constructive skills were assessed using the Judgement of Line Orientation (JLO) (Benton, Varney, & Hamsher, 1978), the Rey Osterrieth Figure copy task and the CLOX part two. Scores reported for the JLO are the number of correct line pairs, with possible scores ranging from 0-30. For the CLOX-II, the examiner first draws a picture of a clock face with the hands on the clock face set at 1.45. The participant is then asked to copy the examiner's drawing.

4.3.5 Statistical Analyses

Differences in demographic and clinical characteristics were examined using Student t tests and χ^2 as appropriate. To assess the magnitude of any differences between the two groups, effect sizes for cognitive impairments were generated using Cohen's *d*. To control for the effect of multiple comparisons, a stringent test of significance was applied ($p < 0.01$) for individual tests. Pearson correlations were employed to assess the association between disease progression and cognitive outcomes and the association between different measures of executive function, visuospatial ability and memory/learning. Z scores were then computed, using the control mean and standard deviation, so that comparisons could be made across tests. Analyses of covariance (ANCOVAs) were used to compare the difference between PD and control scores for a particular cognitive domain while using other domains as covariates. These were considered significant at $p < 0.05$.

4.3.6 Results

Demographic and clinical characteristics

Comparisons between patients with PD and their healthy controls on clinical and demographic characteristics are shown in Table 32. Each of the 40 PD patients included in the main study, was matched as closely as possible to a healthy control in terms of age and pre-morbid IQ. Matching was confirmed by *t* tests (IQ: $t = 0.94$, $df = 78$, $p > .30$; and age: $t = 0.31$ $df = 78$, $p > .75$). Patients with PD had significantly lower MMSE scores and were more likely to endorse symptoms associated with low mood. However, none of the PD patients showed any evidence of clinical depression or dementia. Also, there were significantly more males in the PD group (PD 26/40 [65%] v Control 13/40 [32.5%]) (χ^2 ($df = 1$) = 8.46, $p < .01$). Motor scores for patients with PD varied from mild to severe as measured by the H&Y. However, the patients rated themselves as independent in daily activities as rated by the Modified Schwab and England Activities of Daily Living Scales.

Cognitive outcomes:

Table 33 shows means and standard deviations for patients versus healthy controls and results of *t* tests[2]. Individual *t* tests between PD and healthy controls showed deficits on five out of the seven measures of executive function (Category Fluency, Category Switching, CLOX-I, and Stroop inhibition and inhibition switching). However, there was no significant difference between the two groups in

[2] Due to motor impairments one patient was not able to complete the Key Search, ROF or the CLOX tasks. Due to error one control was not administered the Tower Task and two controls were not administered the Spatial Span task. Three PD patients were not able to return a completed FAQ. However, patients with missing data did not differ from the mean of the PD group in terms of their performance on the DRS-II, MMSE or in terms of years of education and ratings on the H&Y.

terms of planning ability as measured by the Zoo Map and Key search tasks. Patients showed deficits on two of the six measures of problem solving (Matrix Reasoning and SOC's) and two of the three measures of working memory (Reading Span Test, and Spatial Span task). There was no evidence of impairment for either measure of attention (Digits Forward and Backwards).

Table 32: Clinical and demographic characterstics, Parkinson's disease patients versus controls.

	Parkinson's disease (n=40)			**Control Group (n=40)**				
	Mean	SD	Range	Mean	SD	Range	*t*-value	*p*-level
NART[1]	109.05	[10.13]	87-131	111.20	[10.30]	90-128	0.94	>0.30
Education (yrs)[2]	13.94	[2.56]	11-22	13.76	[2.57]	8-20	-0.30	>0.75
Age	66.15	[6.65]	52-77	66.58	[5.47]	52-76	0.31	>0.75
MMSE[3]	28.65	[1.42]	25-30	29.58	[0.71]	28-30	3.67	<0.001*
BDI-II[4]	7.59	[4.34]	0-16	4.13	[3.39]	0-15	-3.96	<0.001*
PD onset[5]	6.49	[4.35]	0.25-23					
UPDRS[6]	28.46	[9.49]	13-49					
S&E[37]	81.0%	[0.10]						
H&Y[8]	Level 1 (n=8)	Level 1.5 (n=6)	Level 2 (n=7)	Level 2.5 (n=10)	Level 3 (n=7)	Level 4 (n=2)		

[1]National Adult Reading Test, [2]Total number of years formal education, [3]Mini Mental Status Exam, [4]Beck Depression Inventory, * significant at p<0.001; [5]Number of years since diagnosis of Parkinson's disease, [6]Unified Parkinson's Disease Rating Scale (motor score component); [7]Modified Schwab and England Activities of Daily Living Scale; [8]Hoehn & Yahr stage.

Consistent evidence of deficits was found for the patient group compared to healthy controls on measures of speed of processing. Two out of the three measures of visuospatial ability were also impaired (ROF copy and CLOX-II). However, there was no significant difference between the groups on measures of memory and learning.

The original analysis was re-run excluding the two patients who had an H&Y of 4 so that the group consisted of only patients with mild to moderate motor impairment. The results remained substantially the same. With these two patients excluded, significance levels for CLOX-I and two of the CANTAB tests, SOC's and Spatial Span were now only significant at $p < 0.05$ (p's <0.04, 0.02 and 0.02, respectively). As the inclusion of these two participants did not change the pattern of impairments for the patients with PD compared to healthy controls, they were included in the analyses.

In terms of effect sizes, for measures with a significant finding in the domain of executive function, these varied from medium to large (d = 0.57-0.88), with an average effect size of 0.77. Significant effect sizes for problem solving (d = 0.63 & 0.69), working memory (d = 1.23 & 0.65) and speed of processing (d = 0.67, 0.95 & 0.76) were all large, with averages of 0.65, 0.94 and 0.79, respectively.

Although some patients in this study were in the moderate to severe range in terms of disease progression, correlations revealed few associations between disease duration or motor symptoms (as measured by the H&Y stage), or mood (as measured by the BDI) and cognitive outcomes. Disease duration was correlated with Paired Associates-II and Color Naming, H&Y stage with Spatial Span, Category Fluency with Color Naming, and mood with Letter Number Sequencing. These associations remained significant after controlling for the effects of age, IQ and years of education.

Table 33: Cognitive Test Outcomes for Parkinson's disease patients versus the healthy control group.

	PD	Controls			Cohen's
	(n=) Mean [SD]	(n=) Mean [SD]	*t* =	*p*-level	*d*
Executive Functioning/Planning					
Verbal Fluency sub-tests: [a]					
• Letter Fluency	(40) 10.53 [3.8]	(40) 12.50 [3.5]	2.44	<0.05	0.55
• Category Fluency	(40) 9.38 [2.5]	(40) 11.75 [3.4]	3.55	<0.001	0.80
• Category Switching	(40) 9.90 [3.6]	(40) 12.43 [3.3]	3.30	<0.01	0.72
CLOX-I	(39) 12.49 [2.6]	(40) 13.65 [1.5]	2.46	<0.01	0.57
Key Search [b]	(39) 2.54 [1.4]	(40) 2.33 [1.3]	-0.70	>0.45	-0.15
Zoo Map [b]	(40) 2.08 [1.9]	(40) 1.90 [1.2]	-0.65	>0.45	-0.17
Color-Word Interference sub-tests:[a]					
• Inhibition	(40) 9.10 [3.3]	(40) 11.58 [2.3]	3.87	<0.001	0.88
• Switching	(40) 9.01 [3.7]	(40) 11.83 [2.3]	3.99	<0.001	0.88
ID/ED- Phases completed [c]	(40) 8.13 [1.6]	(40) 8.48 [0.8]	1.20	>0.20	0.32
Problem solving					
Sorting sub-tests: [a]					
• Card sorting	(40) 10.95 [2.6]	(40) 11.83 [2.7]	1.47	>0.10	0.30
• Card sortingdescription	(40) 10.83 [2.5]	(40) 11.33 [2.8]	0.84	>0.40	0.19
Matrix Reasoning [d]	(40) 53.13 [10.2]	(40) 59.60 [8.5]	3.09	<0.01	0.69
Stockings of Cambridge [c (1)]	(39) 6.6 [2.6]	(39) 8.1 [2.1]	2.82	<0.01	0.63
Tower Test [a (2)]	(39) 4.1 [1.1]	(39) 4.2 [1.2]	0.50	>0.60	0.09
Working Memory/ Attention					
Digits Forward [e]	(40) 10.22 [2.1]	(40) 10.95 [2.3]	1.48	>0.10	0.36
Digits Backwards [e]	(40) 6.38 [2.2]	(40) 7.25 [2.0]	1.86	<0.10	0.43
Letter Number Sequencing [e]	(40) 10.38 [2.6]	(40) 11.65 [2.7]	2.15	<0.05	0.45

Table 33: Continued.

	PD	Controls			Cohen's
	(n=) Mean [SD]	(n=) Mean [SD]	*t* =	*p*-level	*d*
Reading Span Test	(40) 1.66 [0.6]	(40) 2.46 [0.7]	5.73	<0.0001	1.23
Spatial Span [c]	(40) 4.60 [0.7]	(38) 5.18 [1.1]	2.78	<0.01	0.65
Speed of Processing					
Verbal Fluency Test: [a]					
• Word Naming	(40) 10.13 [1.9]	(40) 11.45 [1.8]	3.27	<0.01	0.95
• Color Naming	(40) 9.20 [2.5]	(40) 11.23 [1.6]	4.30	<0.0001	0.76
Memory/Learning					
Logical Memory immediate [e]	(40) 7.85 [3.2]	(40) 8.95 [3.4]	1.50	>0.10	0.30
Logical Memory delayed [e]	(40) 8.63 [3.2]	(40) 9.53 [3.4]	1.21	>0.20	0.27
Paired Associates immediate [e]	(40) 8.00 [2.9]	(40) 9.83 [3.6]	2.50	<0.02	0.55
Paired Associates delayed [e]	(40) 8.40 [2.6]	(40) 9.90 [3.2]	2.28	<0.03	0.51
Auditory Recall index [e]	(40) 8.90 [3.3]	(40) 10.33 [2.6]	2.13	<0.05	0.46
ROF-II&III	(39) 14.65 [6.2]	(40) 17.09 [7.5]	1.57	>0.10	0.35
Visuospatial ability					
ROF-I	(39) 31.87 [4.2]	(40) 34.90 [1.9]	4.14	<0.0001	0.92
Line Orientation	(40) 23.13 [5.4]	(40) 25.40 [3.4]	2.24	<0.05	0.51
CLOX-II	(39) 14.18 [1.1]	(40) 14.78 [0.7]	2.89	<0.01	0.65

(1) Number of towers completed in minimum moves; [a]Delis Kaplan Executive Functioning System standardised scores; [b] Behavioural Assessment of the Dysexecutive Syndrome profile scores;[c] Cambridge Neuropsychological Test Automated Battery;[d] Wechsler Abbreviated Intelligence Scale standardised scores; [e] Wechsler Memory Scale- 3rd edition, standardised scores.

Correlations between cognitive measures are shown in Table 34. All within-domain correlations were significantly positive for problem solving, working memory/attention, speed of processing, memory and learning and visuospatial ability, and for 8 of 10 cases for executive function. To further examine the relationship between each of the domains, scores for each of the measures in the matrix were transformed to *z* scores. These *z* scores were generated using the mean and standard deviation of the control group. Overall scores were then produced separately for each of the five domains by combining the *z* score of measures that differentiated PD patients from controls ($p < 0.01$) divided by the number of measures in each domain. The sixth domain, memory/learning, was included in the matrix for the purpose of comparisons. Paired Associates I & II were combined and Logical Memory I & II were combined, giving a total of three measures that comprised the domain of memory/learning. Correlations for the six domains using these composite scores are shown on Table 35.

Table 34: Correlation between measures of Executive Function, Problem Solving, Working Memory/Attention, Speed of Processing, Memory/Learning and Visuospatial Ability for patients with Parkinson's disease.
(correlations $p<0.01$ highlighted in red).

	Category Fluency	Category Switching	CLOX-I	Inhibition	Inhibition Switching	SOC's [1]	Matrix Reasoning	Spatial Span	Reading Span Test	Stroop Word Reading	Stroop Color Naming	Logical Memory 1&2	Paired Associates 1&2	Auditory Recall Index	ROF-I [2]	CLOX-II
Executive Function																
Category Fluency	1.00															
Category Switching	0.47	1.00														
CLOX-I	0.25	0.38	1.00													
Inhibition	0.46	0.42	0.55	1.00												
Inhibition Switching	0.06	0.49	0.47	0.52	1.00											
Problem Solving																
SOC's [1]	0.28	0.44	0.31	0.55	0.41	1.00										
Matrix Reasoning	0.35	0.47	0.59	0.50	0.45	0.50	1.00									
Working Memory/Attention																
Spatial Span	0.44	0.50	0.48	0.43	0.24	0.30	0.58	1.00								
Reading Span Test	0.14	0.51	0.20	0.19	0.39	0.24	0.24	0.41	1.00							
Speed of Processing																
Stroop Word Reading	0.20	0.45	0.39	0.37	0.56	0.35	0.53	0.39	0.43	1.00						
Stroop Color Naming	0.38	0.49	0.50	0.64	0.38	0.35	0.43	0.38	0.07	0.43	1.00					
Memory/Learning																
Logical Memory 1&2	0.12	0.28	0.24	0.27	0.22	0.48	0.18	0.24	0.30	0.09	0.08	1.00				
Paired Associates 1&2	0.08	0.16	0.17	0.22	0.20	0.04	0.10	0.23	0.10	0.10	0.05	0.34	1.00			
Auditory Recall	0.09	0.29	0.21	0.09	0.24	0.39	0.22	0.15	0.14	0.16	0.08	0.75	0.45	1.00		
Visuospatial Ability																
ROF-I [2]	0.26	0.41	0.55	0.41	0.55	0.26	0.53	0.43	0.24	0.44	0.52	0.05	0.11	0.06	1.00	
CLOX-II	0.04	0.08	0.69	0.19	0.26	0.11	0.43	0.36	0.15	0.32	0.26	0.02	0.05	0.07	0.45	1.00

Table 35: Correlations for between each of the six cognitive domains using scores for Parkinson's disease patients.

	EF[1]	PS[2]	WM[3]	SP[4]	M&L[5]	V[6]
Executive Function	1.00					
Problem Solving	0.69***	1.00				
Working Memory	0.61***	0.46**	1.00			
Speed of Processing	0.71***	0.55***	0.32*	1.00		
Memory/Learning	0.37*	0.36*	0.29	0.05	1.00	
Visuospatial Ability	0.61***	0.47**	0.40***	0.56***	0.06	1.00

[1]Executive Function; [2] Problem Solving; [3] Working Memory; [4] Speed of Processing; [5] Memory/Learning; [6] Visuospatial Ability; significant *p<0.05;**p<0.01;***p<0.001.

As shown in Table 35, executive function and problem solving domains were significantly correlated with all other domains. Memory/learning was the only domain not significantly associated with working memory and visuospatial ability. The domain of memory/learning only showed significant correlations with the two domains of executive function and problem solving.

Separate ANCOVAs were used to control for the effects of memory/learning and visuospatial ability, while assessing the difference between PD group and controls on the domains of executive function, problem solving, working memory, and speed of processing as shown on Table 36.

Table 36: Comparison between patients with Parkinson's disease and healthy controls for the domains of Executive Function, Problem Solving, Working Memory and Speed of Processing after controlling separately for the effects of Memory/Learning and Visuospatial Ability.

	Covariates			
	Memory/Learning		Visuospatial Ability	
	F	*p*	F	*p*
Executive Function	13.16	<0.001***	5.1	<0.05*
Problem Solving	7.86	<0.01**	2.9	>0.10
Working Memory	23.55	<0.0001***	16.29	<0.001**
Speed of Processing	7.43	<0.001**	7.20	<0.01*

Although the differences remained significant for Working Memory and Speed of Processing ($p < 0.01$), Problem Solving and Executive function were no longer significant after controlling for visuospatial ability. However, differences between the two groups remained significant ($p < 0.01$) for all domains after controlling for memory/learning.

ANCOVA's were used separately to control for the effects of executive function, problem solving, working memory and speed of processing (Table 37). There were no significant differences between the PD group and healthy control for the domain of memory/learning. In terms of visuospatial ability, patients with PD remained significantly different from controls regardless of which covariate was entered into the analysis.

Table 37: Comparison between patients with Parkinson's disease and healthy controls for the domains of Memory/Learning and Visuospatial Ability after controlling separately for the effects of Executive Function, Problem Solving, Working Memory and Speed of Processing.

	Covariates							
	Executive Function		Problem Solving		Working Memory		Speed of Processing	
	F	*p*	F	*P*	F	*p*	F	*p*
Memory/Learning	0.57	>0.40	2.35	>0.10	1.04	>0.30	3.25	<0.10
Visuospatial Ability	5.36	<0.05*	9.34	<0.01**	6.09	<0.05*	7.34	<0.01*

4.3.7 Discussion

The purpose of this research was to identify a pattern of cognitive deficits in a group of PD patients without dementia compared to healthy controls. We also examined the relationship between the different domains of cognitive functioning. Parkinson's disease patients showed clear evidence of impaired performance across different aspects of executive functioning and its sub components (working memory, problem solving and speed of processing). We also found evidence of a deficit in visuospatial ability which was independent of aspects of executive function. However, there was no evidence of deficits in measures related to memory/learning, attention, and planning.

Of particular interest was the finding that patients with PD did not show global decline on measures on executive functioning, rather there was evidence of variable performance across the range of measures reflecting executive function abilities. For example, while tests of mental flexibility and inhibition were consistently impaired, as reflected in category and letter fluency tasks and the Stroop tasks, tests that required a

degree of planning showed no impairment. Also, patients with PD appeared to have little difficulty with many of problem solving tasks, with deficits only being observed in tasks that were strongly influenced by visuospatial ability. Differences in the domain of problem solving were no longer significant when visuospatial ability was controlled for. A more consistent pattern of deficits was evident in terms of working memory. Whereas patients showed no deficits on attention-related tasks, they were impaired on three out of the four working memory tasks, with the fourth just failing to reach statistical significance. Although two of the working memory measures required a degree of visuospatial ability (spatial working memory and spatial span), working memory impairment remained significant after visuospatial ability was controlled for.

It has been suggested that any cognitive deficits associated with PD simply reflect the extent of executive function deficits (Taylor & Saint-Cyr, 1995). Therefore, the relationship between executive functions and its subcomponents and memory/learning and visuospatial ability, was also examined. No significant deficits were found for memory/learning and this did not change when different aspects of executive function were controlled for. However, the opposite was found for visuospatial ability. Despite controlling separately for different aspects of executive function, the deficits in visuospatial ability remained significant.

From the large body of literature regarding cognitive outcomes and PD (Pillon, Boller, Levy, & Dubois, 2001), relative to age matched controls, PD patients have been found to have deficits in executive function, inhibition, problem solving, planning, working memory, visuospatial skills and aspects of memory. However, few researchers have specifically examined the different components of executive

function that might be impaired or spared. Nonetheless, the performance across the range of measures reflecting executive function abilities found in this study is consistent with other research that has examined aspects of executive functions in PD patients (Marinus et al., 2003; Muslimovic, Post, Speelman, & Schmand, 2005; Uekermann et al., 2004; Weintraub & Stern, 2005).

There is considerable evidence for deficits in visuospatial function in PD patients without dementia (see Waterfall & Crowe, 1995 for review). However, this relationship has usually been considered to reflect the higher cognitive load generally associated with these tasks. In this study we selected tests that had low cognitive demands and subsequently controlled separately for the effects of executive function and its subcomponents. Bondi et al., (1993) found a result contrary to ours, but tests used in their study were heavily dependent on planning and organisation skills which are associated with executive functions.

The majority of patients in this study were in the mild to moderate range in terms of disease symptoms. However, two of our patients had more severe motor problems. Despite this, correlations revealed few associations between cognitive performance and disease duration or motor symptoms. Further, motor symptoms and disease duration have been reported by a number of groups as an unreliable means of identifying patients who have cognitive problems (Aarsland, Ballard, Larsen, & McKeith, 2001; Cooper, Sagar, Jordan, Harvey, & Sullivan, 1991; Graham & Sagar, 1999; Janvin, Aarsland, Larsen, & Hugdahl, 2003; Lewis et al., 2005; Muslimovic, Post, Speelman, & Schmand, 2005).

The profile of executive function, speed of processing and visuospatial deficits reported here is similar to other recent research regarding cognitive outcomes for PD

patients. One of these recent studies reported outcomes for newly diagnosed patients while another examined patients with advanced PD. Both these studies reported a similar range of cognitive deficits to those found here, even though this study consists of a sample of patients across a wide spectrum in terms of disease severity and duration (Green et al., 2002; Muslimovic, Post, Speelman, & Schmand, 2005). Deficits in executive function, speed of processing and visuospatial ability appear to constitute the core deficits for PD. By comparison, deficits in general memory, planning and attention are much more variable and depend on the methodology of the study and inclusion criteria.

One of the strengths of this study was that a range of measures were used to identify the profile of impaired and spared executive functions. Also, medicated patients across the range of motor impairment who had the dexterity to engage in the testing were included to provide a more representative sample. However, the findings presented here should also be considered in the context of several limitations. Although we endeavoured to recruit a representative sample, patients were self selected and tended to be relatively healthy.

Cognitive impairments are common in PD. A profile characterised by executive function, visuospatial and processing speed deficits has consistently been reported regardless of the disease duration. A unique aspect of this study was the assessment of multiple aspects of executive function, providing evidence regarding intact and impaired executive functions. Identifying the profile of cognitive deficits unique to PD is important as it provides information to clinicians regarding which measures are most appropriate to identify patients who may be experiencing cognitive decline. However, information regarding intact skills is also useful because it may

provide an opportunity to develop appropriate intervention strategies, taking advantage of those aspects of cognitive functioning that have been spared, and that could prolong the independence of patients with PD who are experiencing cognitive decline.

4.3 The Identification of Mild Cognitive Impairment in Parkinson's Disease

4.4.1 Abstract

The goal of this study was to identify sub-groups of PD patients that differed in terms of their cognitive functioning. Data from a broad range of neuropsychological tests and cognitive domains were used in a cluster analysis to identify different sub-groups of PD patients. Resulting sub-groups were then assessed in terms of between-group differences and also compared to individually-matched healthy controls in cognitive functioning and ability to conduct activities of daily living. Three sub-groups of patients were identified that formed a continuum of cognitive impairment from none/mild to severe. Compared to controls, one subgroup showed no or minimal impairment (PD-NCI), a second group showed a more variable pattern of severe and mild impairments (PD-UCI), and a third group had evidence of severe impairment across most of the cognitive domains tested. This latter group was labelled PD-Mild Cognitive Impairment (PD-MCI). The PD-UCI and PD-MCI groups were also significantly different from their controls with respect to their ability to carry out functional activities of everyday living. Results confirm that patients with PD are heterogeneous with regard to their cognitive presentation. Further, the severity of cognitive deficits was not associated with other clinical and demographic characteristics such as motor impairments, age or disease duration. This line of research has considerable clinical utility as it may enable the development of diagnostic criteria for preclinical dementia specific to PD patients (PD-MCI), providing a basis for early intervention that could slow the development of dementia.

4.4.2 Introduction

Cognitive problems have been widely reported in patients with idiopathic Parkinson's disease (PD) and include deficits in visuospatial abilities, speed of mental processing, memory, learning and executive functions (including planning, working memory, attention, verbal function, and decision making) (Pillon, Boller, Levy, & Dubois, 2001). However, the research literature has mixed results regarding the constellation of cognitive deficits that characterize PD. This inconsistency is thought to be due in part to methodological problems and diverse patient group characteristics. But even when these methodological concerns have been addressed, patients have been reported as heterogeneous with respect to their presentation of cognitive symptoms. Thus, more recent research has focused on defining the characteristics of different subgroups of patients as defined by their motor and cognitive characteristics. The identification of these subgroups is important because cognitive deficits in PD have been linked to caregiver distress, reduced quality of life for the patient and early rest home placement (Aarsland, Larsen, Tandberg, & Laake, 2000; Schrag, Jahanshahi, & Quinn, 2000). Furthermore, particular subgroups may be more vulnerable to severe cognitive decline which could signal the onset of dementia. Accurate identification of "at risk" patients would provide an opportunity for interventions that could ameliorate problems associated with cognitive deficits and reduce the associated personal and social costs.

Researchers have examined cognitive outcomes using a number of methods to define subgroup patients, including frontal v non frontal symptoms (Turnbull, Berry, & Bowman, 2003); sporadic v familial PD (Dujardin, Defebvre, Grunberg, Becquet, & Destee, 2001); motor symptoms (Dujardin, Defebvre, Grunberg, Becquet, &

Destee, 2001; Lewis et al., 2005); levels of executive dysfunction (Lewis et al., 2003); and age of onset (Katzen, Levin, & Llabre, 1998). Previous classification systems have frequently been based on intuition and there has been little consensus regarding how different factors interact to disrupt cognitive functions (Graham & Sagar, 1999). Thus more recent research has adopted a "data driven" approach to define subgroups of PD patients (Graham & Sagar, 1999; Lewis et al., 2005). Methods such as cluster analysis, as used by these authors, have the advantages of avoiding arbitrary cut-offs and predetermined classification systems, and enabling discrete sub-groups to be identified so that all within a given group are maximally similar.

Graham and Sagar (1999) used information regarding demographic, motor, mood and cognitive performance in a cluster analysis to identify different sub-groups in a convenience sample of 176 patients with PD. Three separate clusters were identified: 1) a group with motor impairment only and no intellectual impairment; 2) a group with both motor and cognitive impairments; and 3) a group with rapidly progressing motor and cognitive symptoms. The latter group tended to be older at disease onset.

Lewis et al. (2005) obtained information regarding mood, motor and cognitive functioning from 120 patients in the early clinical stages of PD (Hoehn and Yahr stages I&II) and performed a cluster analysis. Four separate sub-groups were identified with different characteristics: 1) younger age at disease onset; 2) tremor dominant with mood and cognitive impairment; 3) non-tremor dominant; and 4) a group with rapid disease progression but no cognitive impairment. However, many of the variables studied by these researchers were based on motor impairment. Because the relationship between motor impairment and cognitive symptoms is inconsistent

(Graham & Sagar, 1999; Janvin, Larsen, Aarsland, & Hugdahl, 2006; Lewis et al., 2005; Mahieux et al., 1998) use of these variables may obscure the identification of sub-groups of patients with different cognitive characteristics including those at the stage of preclinical dementia or mild cognitive impairment.

The term "mild cognitive impairment" (MCI) has been used in the dementia literature to describe cognitive deficits that are greater than those associated with normal aging, but not sufficiently severe to warrant a diagnosis of dementia (Petersen, 2004; Petersen et al., 2001). Individuals with MCI are more at risk of developing Alzheimer's disease (AD). Although the concept of MCI has not been widely studied in relation to PD, there are reasons to expect that it might be useful for identifying those patients that are more likely to progress to dementia. For example, a recent study by Janvin et al. (2006) used the concept of MCI to examine progression of cognitive decline in 59 non-demented PD patients. Two groups of patients were defined: Those showing signs of MCI (n=29) according to the criteria suggested by Petersen, and those who were cognitively intact (n=30). The MCI group was further divided into 3 subgroups according to their cognitive profile (MCI amnestic type, MCI single domain impaired non-memory and MCI multiple domains slightly impaired). At the four-year follow-up, 62% of patients with MCI and 20% of cognitively intact patients were diagnosed as having dementia. Single domain non-memory and multiple domains slightly impaired were associated with the development of PDD, whereas MCI amnestic was not. However, the range of cognitive domains assessed by Janvin et al. was limited, making it difficult to ascertain the specific impairments that might be associated with PD-MCI.

The question of whether Parkinson's disease with MCI (PD-MCI) represents a distinct clinical entity that includes those patients who will progress to PDD requires further investigation. The aim of the present study was to use a data-driven method to identify subgroups of patients with PD that differed in terms of cognitive functioning. Compared to previous studies (Graham & Sagar, 1999; Janvin, Larsen, Aarsland, & Hugdahl, 2006; Lewis et al., 2005), a broad range of neuropsychological tests were used, that assessed various domains of cognitive functioning. We hypothesized that if PD-MCI represents a distinct subtype, then a cluster analysis should reveal not only those patients comprising the PD-MCI group, but the specific subset of tests that was most indicative of patients with PD-MCI. To test this hypothesis, it was planned to determine whether the subset of tests that best differentiated among subgroups of PD patients was the same subset that differentiated the PD patients overall from healthy matched controls. As secondary goals, it was planned to identify the clinical and demographic characteristics of any resulting subgroups, and to determine whether these differed in terms of impairments in daily living. It would be expected that if a subgroup of patients with a pattern of cognitive impairment analogous to MCI associated with AD were found, that the resulting deficits would have begun to interfere with their ability to cope appropriately with activities of daily living.

4.4.3 Methods

Approval for this study was granted by the Canterbury Ethics Committee and informed consent was obtained from patients and control participants.

Participants

Parkinson's disease group

Parkinson's patients in the Canterbury region, with a diagnosis of idiopathic PD (diagnoses were confirmed by a neurologist who specialised in movement disorders), who could be identified at the time of this study and had not been diagnosed with dementia, were invited by letter to participate. Inclusion/exclusion criteria were as follows: Inclusion criteria: 1) Assessed at the Hoehn & Yahr stage I-IV; 2) Aged between 50 and 80 years; 3) Adequate or corrected hearing and vision (self report checked by examiner); 4) Stable on PD medication; 5) English as the primary spoken language. Exclusion criteria were: 1) Currently involved in a therapeutic trial; 2) History of: a) moderate or severe head injury; b) stroke or other neurological impairment; c) major medical illness; d) significant psychiatric illness requiring hospitalisation; e) suspicion of dementia symptoms (MMSE <25); f) diagnosis of, or special education for, a learning disability; g) major depressive episode in the previous 6 months; 3) Pre-morbid IQ estimated at <85 using National Adult Reading Test (NART); 4) Currently taking medications known to have a significant effect on Central Nervous system (other than medications prescribed for the control of PD symptoms); 5) Beck Depression Inventory –II score of >17.

Of the 115 letters that were mailed, 6/115 (5.2%) of individuals with PD could not participate due to illness, 6/115 (5.2%) were deceased, 8/115 (6.9%) declined, 34/115 (29.6%) did not respond, and 21/115 (18.3%) did not meet the inclusion/exclusion criteria. After exclusions, 40 participants with PD were included in the analyses.

Controls

Controls were recruited from a number of sources including a previously established data base, advertisements at local clubs (bowling, hiking and table tennis) and businesses. All controls were given a brief outline of the study on first phone contact. If they were still willing to participate they were then sent an information sheet. In addition to adequate or corrected hearing and vision (self report, checked by the examiner) and being aged between 50 to 80 years of age, the same exclusion criteria listed above also applied to the control group.

4.4.4 Procedure

Assessments were carried out at the University of Canterbury over three testing sessions, each of three hours duration. Tests were presented in a fixed order with breaks taken as required. Patients with PD were tested while on optimal levels of medication (based on patient report). Information pertinent to the inclusion/exclusion criteria was elicited from all participants using a semi-structured interview.

Participants were also asked to nominate a person who knew them well (a "significant other") to provide collateral information regarding their daily living activities. If the participants agreed, the significant other was contacted, the purpose of the study was explained, and consent obtained. In most cases the significant other was a spouse or other family member.

In the case of control participants, information for the significant others to complete was sent home with the participant and returned at the next testing session. For PD patients, information regarding everyday activities was collected during a

face-to-face interview with a significant other person. In the majority of cases, these interviews were conducted by a second interviewer during the same time period that the patient was engaged in the second or third testing session.

Clinical Assessment

To ensure that none of the patients included in the study met the criteria for dementia, the Dementia Rating Scale (DRS-2) (Jurica, 2001) was used in addition to the MMSE. This scale consists of 36 tasks and five subscales. The five subscales provide information on specific abilities and include: 1. Attention; 2. Initiation/ Perserveration; 3. Construction ability; 4. Conceptualization; and 5. Memory. Based on normative data, raw scores from each subscale were summed to provide an overall score (ranging from 0-144 with higher scores indicating better performance) A DRS-II score of 130 has previously been validated as appropriate for PD patients (Brown et al., 1999). However, as pointed out by Green et al (Green et al., 2002) this may exclude some patients due to motor deficits. Therefore, patients with a total raw score of <120 were excluded and those with raw scores between 120 and 130 were further assessed for dementia by a registered clinical psychologist using the Diagnostic and Statistical Manual of Mental Disorders-IV (DSM-IV) criteria. Two patients scored below 130 but neither patient met the DSM-IV criteria for dementia. A combined scaled score adjusted for age and education was then generated using a regression formula provided in the administration manual (Jurica, 2001).

Two scales were used to provide information regarding motor impairment: 1) The Hoehn and Yahr and 2) the Unified Parkinson's Disease Rating Scale (UPDRS) (Goetz et al., 1995). Three scores were generated using the UPDRS, a) The severity of motor symptoms was rated using the motor section; b) a tremor score calculated as

the average of items 16 and 20-26 on the UPDRS; and c) a non tremor score calculated as the average of items 5,7,12-15, 18, 19, and 27-44 and divided by 26 (Lewis, Dove, Robbins, Barker, & Owen, 2003). The Hoehn and Yahr (H&Y) scale was used to rate the stage of the disease (Hoehn & Yahr, 1967).

Cognitive tests used in the cluster analysis

Tests from six cognitive domains were included in the cluster analysis: 1) General executive function/planning; 2) problem solving; 3) working memory/attention; 4) speed of processing; 5) memory/learning; and 6) visuospatial ability.

All tests were commonly used neuropsychological measures and scored according to standard procedures. The majority of the measures used were from standardized batteries including the Wechsler Abbreviated Scale of Intelligence (WASI) [Mean 50, Standard deviation10], (Wechsler, 1997) the Delis Kaplan Executive Function System (D-KEFS),(Delis, Kaplan, & Kramer, 2001) and the Wechsler Memory Scale-III (WMS-III)(Wechsler, 1997) [both mean 10, standard deviation, 3] with age-adjusted norms. Such norms were not available for tests from the Behavioral Assessment of the Dysexecutive Syndrome (BADS) [scores range from 0-4], (Wilson, Alderman, Burgess, Emslie, & Evans, 1996) Cambridge Neuropsychological Test Automated Battery (CANTAB),(Owen et al., 1992) Reading Span task, and tests of visuospatial functioning.

Executive function and planning skills were evaluated using the following test from the D-KEFS: Verbal Fluency test (with subtests for letter fluency, category fluency and category fluency switching) and Color-Word Interference test (with sub-tests for Inhibition and Inhibition switching). Also included in this domain were the

Key Search and Zoo map from the BADS, the Intradimensional/Extradimensional Shift (ID/ED) from the CANTAB (Owen et al., 1992) (number of stages completed, scores vary from 0-9) and the CLOX-I (scores range from 0 to 15, with higher scores indicating better performance) .(Royall, Cordes, & Polk, 1998).

Problem solving was assessed using the Card Sorting subtest sorting recognition, and the Tower Task (number of towers completed in the minimum number of moves, maximum score possible 9), both from the D-KEFS, Matrix Reasoning subtest from the WASI, and the Stockings of Cambridge (SOC's) from the CANTAB (Owen et al., 1992) (number of towers completed in the minimum number of moves, maximum score possible 12).

Working memory/attention was assessed using Letter Number Sequencing, and Digits Forward and Backward from the WMS-III, Spatial Span (maximum sequences correctly recalled 0-9) from the CANTAB and the Daneman and Carpenter Reading Span test (scores range from 1-6) (Daneman & Carpenter, 1980). Speed of Processing was evaluated using Word Naming and Color Naming from the D-KEFS Color-Word interference test.

Memory/learning was assessed with the WMS-III, Paired Associates (immediate and delayed), Logical Memory (immediate and delayed) and the Auditory Recall Index. The Rey Osterrieth Figure (ROF) recall after 3 (ROF-I) and 30 minutes (ROF-II) was also used as a measure of memory ability.

Visuospatial/constructive skills were assessed using the Judgement of Line Orientation (JLO); scores are number of correct line pairs, with possible scores ranging from 0-30 (Benton, Varney, & Hamsher, 1978). Also included in this domain were the Rey Osterrieth Figure copy task and the CLOX part two. All three parts of

the ROF are rated the same, scores range from 0-36, with higher scores indicating more accurate performance (Spreen & Strauss, 1998).

Information regarding everyday living

Functional Activities Questionnaire (FAQ) (Pfeffer, Kurosaki, Harrah, Chance, & Filos, 1982) was used to assess patients' functional capacity and included items such as ability to prepare a balanced meal or remembering appointments. The questionnaire was completed by a significant other who rated the patients on their ability to complete 10 higher-order tasks according to a 4 point scale (dependent = 3, requires assistance = 2, has difficulty but does by self = 1, no difficulty = 0). A total score for the FAQ is obtained by summing the scores across the 10 items (Pfeffer, Kurosaki, Harrah, Chance, & Filos, 1982).

4.4.5 Statistical Analysis

Non-hierarchical (k-means) cluster analyses were performed on the 40 PD patients with two, three and four cluster solutions. Analyses were conducted using the 26 tests covering all six cognitive domains (although patients were tested on a total of 29 tests, only 26 tests were completed by all patients and these were used in the cluster analysis[3]) and again using 13 cognitive tests that differentiated PD patients significantly from healthy controls ($p< 0.01$) Differences in demographic and clinical characteristics for the resulting subgroups were examined using analysis of variance (ANOVA). Measures were then transformed to z-scores, using the control means and standard deviations, so that comparisons could be made across tests. To control for

[3] Due to motor impairments one patient was not able to complete the Key Search, ROF or the CLOX tasks. Due to error one control was not administered the Tower Task and two controls were not administered the Spatial Span task. Three PD patients were not able to return a completed FAQ. However, patients with missing data did not differ from the mean of the PD group in terms of their performance on the DRS-II, MMSE or in terms of years of education and ratings on the H&Y.

the effect of multiple comparisons, $p < 0.01$ was considered significant for individual tests. Finally, Student *t*-tests were used to compare each of the groups identified in the cluster analysis with their matched controls for cognitive outcomes and in terms of deficits in daily living.

4.4.6 Results

Figure 6 shows the results of the cluster analyses for 2, 3 and 4 cluster solutions using 26 and 13 variables. Analysis of the 2, 3 and 4 cluster solutions for the 26 variables shows that groupings were consistent (Figure 6A). Because the fourth group in the 4 cluster solution comprised only two patients, a final three cluster solution was forced by combining the yellow and red groups. Table 38 displays the results of the ANOVAs for the resulting three groups for the full set of 29 variables. Numbers 1-13 on Table 38 indicate tests that are significant for PD patients versus matched control at $p < 0.01$.

ANOVAs found significant differences ($p < 0.01$) across the PD subgroups for 10 of these 13 measures (77%). Of the remaining 16 variables which were not differentiated between PD patients and matched controls, significant ANOVA results were obtained in just 3 cases (18.8%). This confirms that the variables which were most indicative of heterogeneity in cognitive functioning among PD patients were largely the same variables that differentiated PD patients from healthy controls, as predicted by the hypothesis that there is a subgroup of PD patients with cognitive impairment. Because we were interested in identifying the most discriminating tests that could easily be used by clinicians to identify PD-MCI, we re-ran the analysis with just the 13 variables previously found to differentiate the PD patients and matched

controls. This analysis yielded essentially the same clusters with 90% of cases remaining in their respective groups (see Figure 6B).

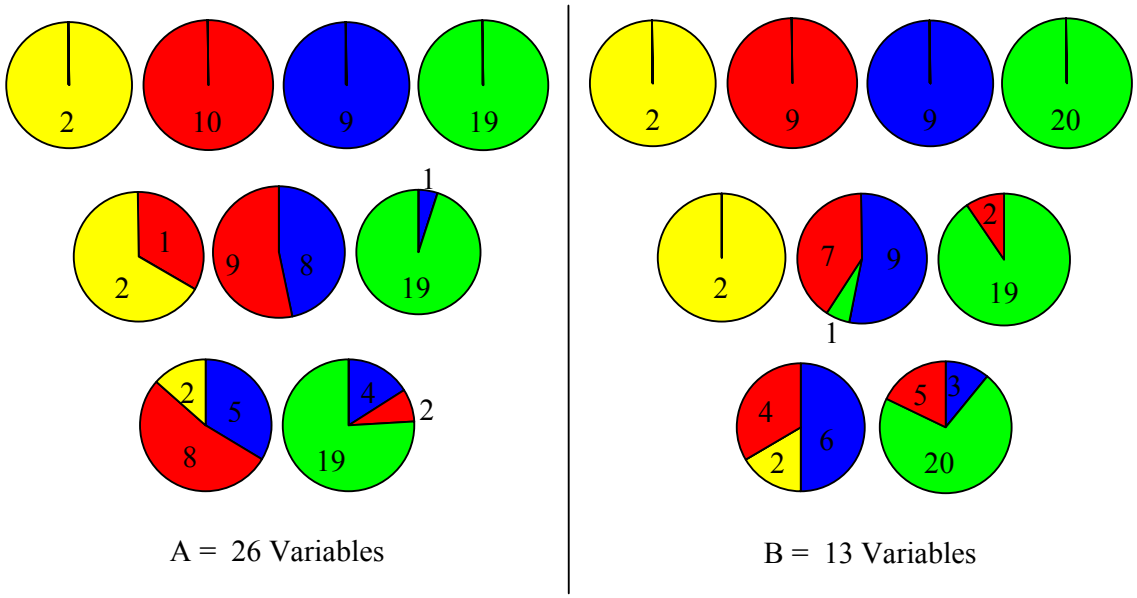


Figure 6: Different patient combinations for two, three and four cluster solutions using 26 variables (panel A) and then with the 13 variables (panel B) previously found to be differentially sensitive to impairments for Parkisons' disease versus healthy controls.

Table 38: Comparison between the three Parkinson's disease groups identified by the cluster for cognitive characteristics.

	∫	Green group N=19 Mean [SD]	Blue group N=9 Mean [SD]	Red group N=12 Mean [SD]	F	*p*-level*
Executive Functioning/Planning						
Verbal Fluency sub-tests: [a]						
• Letter Fluency		12.95 [3.0]	10.33 [2.8]	6.83 [2.1]	18.15	**<0.001**
• Category Fluency	**1**	10.21 [2.5]	9.67 [2.3]	7.83 [2.3]	3.73	<0.05
• Category Switching	**2**	11.42 [3.2]	10.89 [2.0]	6.75 [3.1]	9.70	**<0.001**
CLOX-I	**3**	13.89 [1.4]	10.89 [1.9]	11.36 [3.4]	7.48	**<0.01**
Key Search [b]		2.95 [1.1]	1.89 [1.5]	2.36 [1.6]	2.04	>0.10
Zoo Map [b]		2.47 [1.0]	1.89 [1.5]	1.58 [1.1]	2.38	>0.10
Color-Word Interference subtest[a]						
• Inhibition	**4**	10.63 [2.3]	10.00 [1.9]	6.00 [3.5]	11.79	**<0.001**
• Switching	**5**	10.90 [2.3]	10.11 [2.6]	5.42 [3.9]	13.84	**<0.001**
ID/ED- Phases completed [c]		8.58 [0.8]	8.44 [2.5]	7.17 [2.5]	3.31	<0.05
Problem solving						
Card Sorting Description		12.32 [2.1]	10.89 [1.6]	8.42 [1.9]	15.00	**<0.001**
Matrix Reasoning [d]	**6**	60.16 [5.7]	49.00 [8.7]	45.08 [9.4]	15.89	**<0.001**
Stockings of Cambridge [c (1)]	**7**	7.42 [2.2]	7.67 [1.5]	4.58 [2.8]	7.01	**<0.01**
Tower Test [a (2)]		4.39 [1.1]	3.67 [0.7]	3.92 [1.2]	1.56	>0.20
Working Memory/ Attention						
Digits Forward [e]		11.00 [2.4]	9.56 [1.9]	9.50 [1.4]	2.59	<0.10
Digits Backwards [e]		7.58 [2.4]	5.22 [1.6]	5.33 [1.3]	6.80	<0.05
Letter Number Sequencing [e]		11.21 [2.8]	10.67 [0.7]	8.83 [2.7]	3.47	<0.05
Reading Span Test	**8**	1.79 [0.6]	1.78 [0.7]	1.38 [0.4]	2.32	>0.10
Spatial Span [c]	**9**	4.89 [0.5]	4.56 [0.5]	4.17 [0.8]	5.30	**<0.01**

Table 38 continued.

	∫	Green group N=19 Mean [SD]	Blue group N=9 Mean [SD]	Red group N=12 Mean [SD]	F	*p*-level*
Speed of Processing						
Verbal Fluency Test: [a]						
• Word naming	**10**	10.95 [1.7]	9.78 [2.0]	9.08 [1.4]	4.56	<0.02
• Color naming	**11**	10.58 [1.5]	8.78 [2.4]	7.33 [2.7]	8.71	**<0.001**
Memory/Learning						
Logical Memory immediate [e]		7.68 [3.0]	9.56 [1.9]	6.83 [4.0]	2.01	>0.10
Logical Memory delayed [e]		8.95 [3.1]	10.00 [2.7]	7.08 [3.3]	2.50	<0.10
Paired Associates immediate [e]		8.00 [3.1]	9.22 [3.4]	7.08 [3.0]	1.38	>0.20
Paired Associates delayed [e]		8.68 [2.8]	8.56 [2.1]	7.83 [2.9]	0.39	>0.60
Auditory Recall index [e]		9.42 [3.0]	10.56 [2.3]	6.83 [3.6]	4.30	<0.05
ROF-II&III		17.08 [6.4]	11.83 [4.5]	12.77 [5.9]	3.22	<0.10
Visuospatial ability						
ROF-I	**12**	34.58 [1.7]	29.28 [3.4]	29.32 [5.1]	12.04	**<0.001**
Line Orientation		27.00 [2.2]	20.00 [4.4]	19.33 [5.9]	16.86	**<0.001**
CLOX-II	**13**	14.74 [0.6]	12.89 [0.9]	14.27 [1.2]	14.12	**<0.001**

∫ Bold numbers indicate tests that are significant at $p < 0.01$ for PD v Healthy controls, [1]Number of towers completed in minimum moves; [a]Delis Kaplan Executive Functioning System standardized scores; [b] Behavioral Assessment of the Dysexecutive Syndrome profile scores;[c] Cambridge Neuropsychological Test Automated Battery;[d] Wechsler Abbreviated Intelligence Scale standardized scores; [e] Wechsler Memory Scale- 3rd edition, standardized scores.

In terms of specific cognitive domains, significant differences among the PD subgroups were found for 5 out of 9 measures of executive function including verbal fluency (category fluency, and category switching), the CLOX-I and measures of inhibition (see Table 38). The groups also varied on 3 of 4 measures of problem solving (Card Sorting Description, Matrix Reasoning and Stockings of Cambridge), 1

of 4 working memory measures (Spatial Span), and all measures used to test speed of processing and visual spatial ability (all *p's* < 0.01). None of the measures used to assess memory/learning showed evidence of deficit across all three groups. There was no difference between the groups in terms of attention as measured by Digits Forward.

ANOVAs were used to examine the clinical and demographic characteristics for the three PD groups (Table 39). As might be expected, given their different levels of cognitive impairment, the groups showed significant differences in terms of current mental status as measured by the MMSE. The only other significant differences between the groups were obtained for one measure of premorbid ability. Patients in the PD-UCI and PD-MCI group had lower pre morbid intelligence, ($F = 17.45$, $df = 37$, $p < 0.001$).

Table 39: Comparison between the three Parkinson's disease groups identified by the cluster analysis for clinical and demographic characteristics.

	PD-NCI N=19 Mean [SD]	PD-UCI N=9 Mean [SD]	PD-MCI N=12 Mean [SD]	F	*p*-level
MMSE[1]	29.32 [0.8]	28.77 [1.0]	27.50 [1.8]	8.27	**<0.01**
DRS-II[2]	10.52 [2.1]	10.29 [1.6]	9.16 [3.7]	1.03	>0.30
Years of Education	15.13 [0.1]	12.89 [1.8]	12.83 [1.0]	4.67	<0.05
NART[3]	116.37 [7.3]	103.33 [7.9]	101.75 [7.4]	17.45	**<0.001**
Age	64.37 [6.6]	66.00 [7.4]	69.08 [5.5]	1.94	>0.10
UPDRS Total [4]	26.68 [6.0]	28.11 [11.1]	31.82 [12.6]	1.03	>0.30
UPDRS Tremor	0.57 [0.3]	0.42 [0.3]	0.66 [0.6]	0.96	>0.30
UPDRS Non Tremor	1.07 [0.3]	1.21 [0.5]	1.32 [0.5]	1.46	>0.20
PD Onset[5]	5.79 [3.0]	6.33 [2.9]	7.84 [6.1]	0.77	>0.47
H&Y[6]	2.03 [0.7]	2.05 [0.8]	2.33 [1.0]	0.54	>0.50
BDI-II[7]	7.68 [4.5]	8.22 [5.2]	6.92 [3.5]	0.24	<0.79

[1] Mini Mental Status Exam; [2] Mattis Dementia Rating Scale adjusted for age and education; [3] Premorbid intelligence estimate using the National Adult Reading Test; [4]Unified Parkinson's disease rating scale motor score; [5] Number of years since Parkinson's disease was first diagnosed; [6] Hoehn & Yahr stage; [7] Beck Depression Inventory-II.

Figure 7 displays the comparison between the three groups of PD patients identified in the cluster analysis using z-scores for the 13 measures that were found to be significantly different at $p < 0.01$ (see Table 38). The graph shows that the three PD groups represent a continuum of overall cognitive impairment, from minimal/no

cognitive impairment (PD-NCI), uncertain cognitive impairment (PD-UCI), to mild cognitive impairment (PD-MCI), rather than impairments on different subsets of tests.

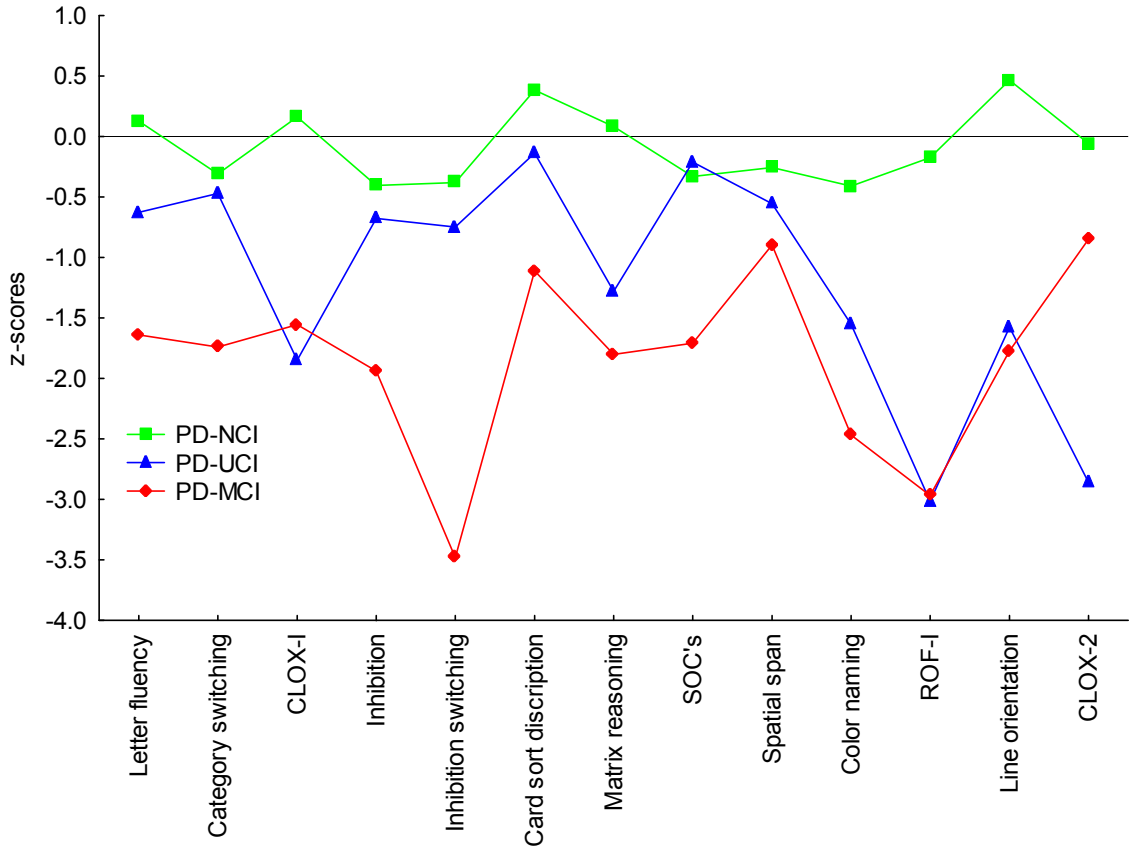


Figure 7: Comparison between the three groups of Parkinson's disease patients identified in the cluster analysis using the 13 measures that showed significant differences ($p<0.01$) across groups.

Table 40 shows the medications used by the patients according to their respective subgroups. The only notable differences were that patients in the PD-UCI and PD-MCI groups were more likely to be using MAO-B Inhibitors and patients in the PD-NCI and PD-MCI group were more likely to be using anticholinergic medication.

Table 40: Medications used by each of the 3 sub-groups identified by the cluster analysis.

	PD-NCI % (n=19)	PD-UCI % (n=9)	PD-MCI % (n=12)
L-Dopa	47.4 % (9/19)	66.7% (6/9)	66.7% (8/12)
Anticholinergics	68.4% (13/19)	11.1% (1/9)	41.7% (5/12)
Dopamine Agonists	52.6% (10/19)	44.4% (4/9)	50.0% (6/12)
COMPT Inhibitor[1]	5.3% (1/19)	11.1% (1/9)	8.3% (1/12)
MAO-B Inhibitor[2]	15.8% (3/19)	44.4% (4/9)	66.7% (8/12)

[1] Catechol-O-methyl-tranferase Inhibitor; [2]monoamine oxidase type-B Inhibitor

Figure 8 shows a comparison of performances on the different cognitive tests for the three PD subgroups with healthy controls. Each of the 40 PD patients was matched as closely as possible to a healthy control in terms of age and pre-morbid IQ (McKinlay, Grace, Dalrymple-Alford, & Roger in review). Matching was confirmed by *t* tests (IQ: $t = 0.94$, $df = 78$, $p > 0.30$; and age: $t = 0.31$ $df = 78$, $p > 0.75$). As shown in Figure 8 (panel A), for the PD-NCI group, significant differences ($p < .01$) with their matched controls were found for 2 out of 29 measures, Reading Span (t=3.62, df, 36) and Paired Associates I (t=2.85 $df = 36$) in two separate domains, Working Memory and Memory/Learning. The PD-UCI group, (panel B) had deficits over four domains, Working Memory, Executive function, Speed of Processing and Visuospatial skills (specific deficits included: CLOX-I ($t = 4.81$, $df = 16$), Color Naming ($t = 3.10$, $df = 16$), ROF-I ($t = 4.98$, $df = 16$), and CLOX-II ($t = 6.83$, $df = 16$)).

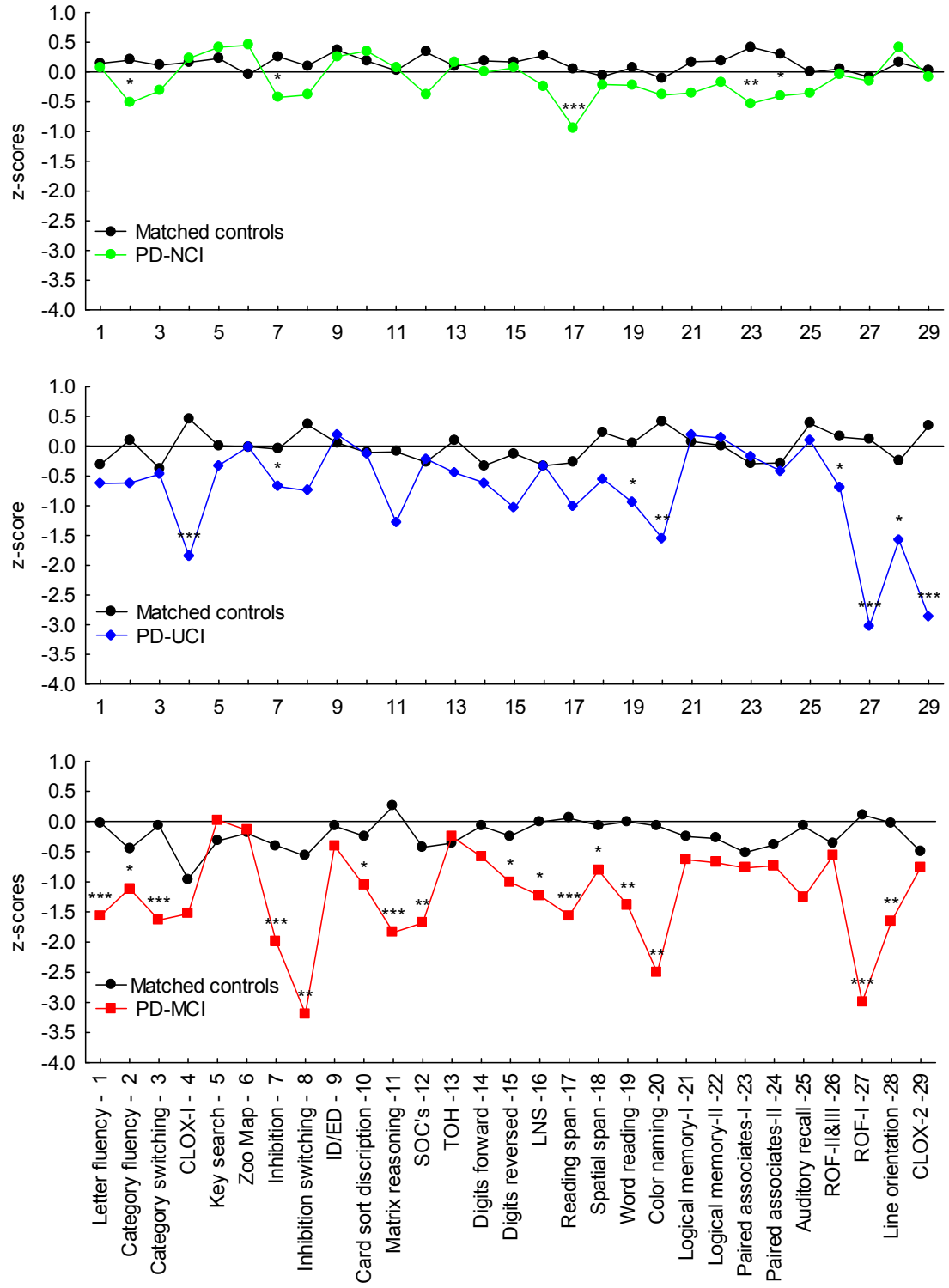


Figure 8: Comparison between Parkinson's disease patients and matched controls on measures of cognitive functioning at time one. *= $p<0.05$; **= $p<0.01$; ***=$p<0.001$.

By contrast, the PD-MCI groups, (panel C) showed deficits across 5 of the 6 domains compared to matched controls (the exception being Memory/Learning). Specific measures that showed a significant difference ($p < .01$) included Letter Fluency ($t = 5.27$, $df = 22$), Category Switching ($t = 5.08$, $df = 22$), Inhibition ($t = 4.18$, $df = 22$), Inhibition Switching($t = 3.77$, $df = 22$), Matrix Reasoning ($t = 4.00$, $df = 22$), SOC's ($t = 2.97$, $df = 22$), Reading Span ($t = 4.80$, $df = 22$), Word Reading ($t = 3.18$, $df = 22$), Color Naming ($t = 4.16$, $df = 22$), ROF-I ($t = 3.82$, $df = 22$) and Line Orientation ($t = 3.08$, $df = 22$).

Using a criterion that has been used in previous reports, mild cognitive impairment was defined as ≤ 1 SD and severe cognitive impairment ≤ 2 SD below the control group norm. (Woods & Troster, 2003) Across the PD-NCI, PD-UCI, and PC-MCI subgroups, there was a trend for an increasing number of patients to exhibit severe deficits on at least one cognitive domain (see Table 4). Moreover, whereas the PD-NCI group showed evidence of deficits over two domains (working memory and memory/learning; see Figure 3) the deficit for one of the domains, memory/learning, was generated by a mild decline for the majority of the individuals in the groups as opposed to evidence of severe deficits (Table 4). There was clear evidence of severe deficits in four domains for the PD-UCI group (executive function, speed of processing, working memory, and visuospatial ability) and five domains for the PD-MCI group (executive function, speed of processing, problem solving, working memory, and visuospatial ability).

All PD patients and 90% of the control group showed a mild and or severe deficit on at least one measure over one or more of the six cognitive domains.

However, PD patients were more likely to show increased evidence of severe deficits (see Table 41).

Table 41: Number and percentage of Parkinson's disease patients versus matched controls who exhibited deficits separately for each of the six domains.

	Mild Deficits >1SD[1] n (%)			Severe Deficits >2SD [1] n (%)		
	NCI[2] n=19	UCI[3] n=9	MCI[4] n=12	NCI n=19	UCI n=9	MCI n=12
Executive function						
PD patients	12 (63.2)	5 (55.6)	0 (0.0)	4 (21.1)	**4 (44.4)**	**12 (100.0)**
Matched controls	7 (36.8)	4 (44.4)	6 (50.0)	3 (15.8)	0 (0.0)	4 (33.3)
Problem Solving						
PD patients	7 (36.8)	6 (66.7)	4 (33.3)	1 (5.3)	2 (22.2)	**7 (58.3)**
Matched controls	5 (26.3)	4 (44.4)	7 (58.3)	1 (5.3)	0 (0.0)	0 (0.0)
Working memory						
PD patients	8 (42.1)	3 (33.3)	5 (41.7)	**5 (26.3)**	**4 (44.4)**	**7 (58.3)**
Matched controls	7 (36.8)	4 (44.4)	7 (58.3)	2 (10.5)	1 (11.1)	1 (8.3)
Speed of processing						
PD patients	7 (36.8)	5 (55.6)	3 (25.0)	1 (5.3)	**3 (33.3)**	**8 (66.7)**
Matched controls	5 (26.3)	1 (11.1)	2 (16.7)	1 (5.3)	0 (0.0)	0 (0.0)
Memory/learning						
PD patients	10 (52.6)	4 (44.4)	8 (66.7)	**2 (10.5)**	0 (0.0)	3 (25.0)
Matched controls	9 (47.4)	5 (55.6)	6 (50.0)	0 (0.0)	0 (0.0)	2 (16.7)
Visuospatial ability						
PD patients	7 (36.8)	0 (0.0)	0 (0.0)	2 (10.5)	**9 (100.0)**	**12 (100.0)**
Matched controls	4 (21.1)	1 (11.1)	4 (33.3)	5 (26.3)	0 (0.0)	2 (16.7)

[1]If any patient or control had both a mild and severe deficit in a given domain they were counted as severe; [2] minimal cognitive impairments; [3] intermediate or uncertain cognitive impairment; [4] "Mild Cognitive Impairment" Bold numbers for severe deficits indicate the domains that were significantly impaired compared to controls (see Figure 3).

To provide a summary comparison, measures within each domain were averaged across participants and groups. Results are shown in Figure 9. There is evidence for increasing deficits across the three subgroups.

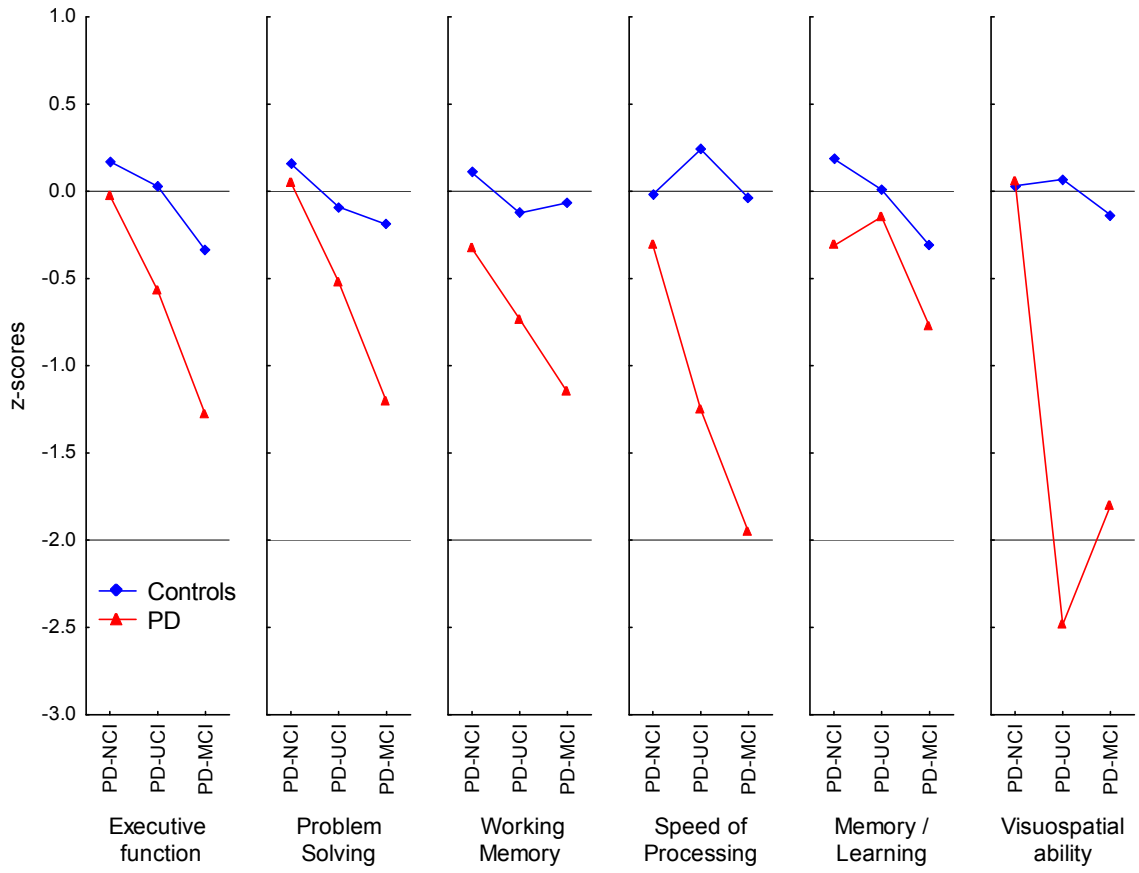


Figure 9: Comparisons between Parkinson's disease patients and their matched controls for each of the six cognitive domains.
(z-scores were generated by averaging all measures separately from each domain listed on Table 38, with the exception of Digits Forward which forms the domain of attention).

Difficulties with daily living, as measured by the Functional Activities Questionnaire, are shown in Figure 10 for the PD subgroups and matched controls. The PD-UCI ($t = -2.59$, $p < 0.05$) and PD-MCI ($t = -3.05$, $p < 0.01$), subgroups had

more difficulties with everyday tasks than matched controls. By contrast, there was no significant difference between the PD-NCI group and their controls.

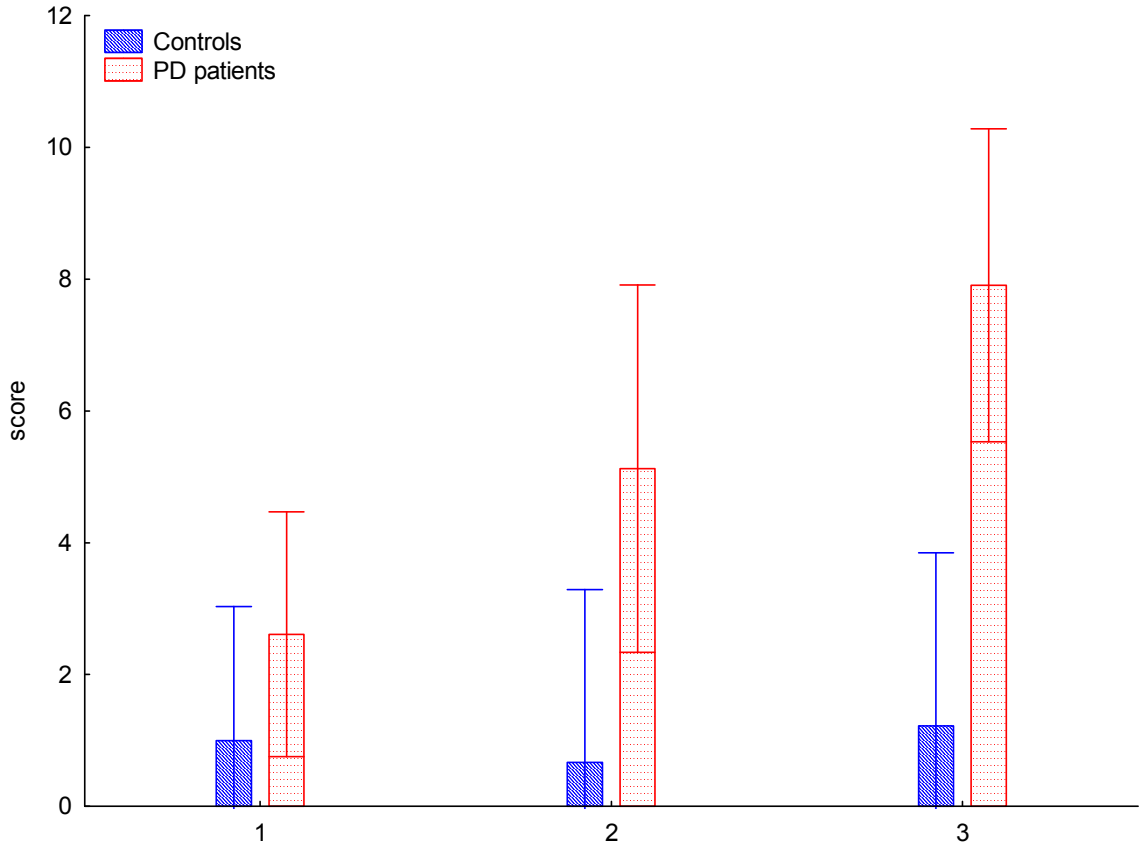


Figure 10: Comparison between the three groups of Parkinson's disease patients and between each group of patients and their matched controls using the Functional Activities Questionnaire.

(Only 37 Parkinson's disease patients (PD-NCI n=18; PD-UCI n=8; PD-MCI n=11) and 33 controls (15, 9 and 9 respectively) completed this questionnaire). * $p<0.05$; ** $p<0.01$.

4.4.7 Discussion

This study used a data-driven method to identify different sub-categories of cognitive impairment for patients with PD. Twenty-nine commonly used neuropsychological tests, covering six cognitive domains, were administered to a group of PD patients. We found that predominately the same variables that differentiated the PD patients overall from the healthy controls, were those that were associated with heterogeneity among PD subgroups.

Differences among the PD subgroups were found for measures of executive function, problem solving, working memory, speed of processing, and visual spatial ability. There was no difference between the groups in terms of memory/learning or attention. Comparisons of these subgroups indicated that the groups represented a continuum of cognitive impairment (see Figures 7 and 9) ranging from none or minimal (which were labelled PD with No Cognitive Impairment (PD-NCI)) to PD patients with a more varied pattern of cognitive impairment which included areas of severe impairment (which were labelled as PD with Uncertain Cognitive Impairment (PD-UCI)) through to PD patients who were showing evidence of multiple domains with severe cognitive impairments but did not meet the criteria of dementia (PD-MCI). Taken together with the consistency of the tests which differentiated the PD patients from the healthy controls and were associated with heterogeneity across the PD subgroups, this suggests that MCI is an identifiable syndrome that affects a subset of PD patients. Clinical and demographic characteristics were also examined and subgroups of patients were found to be similar in terms of medications used, motor impairments, age, and mood.

Because groups varied on some premorbid abilities, we also compared patients to matched controls. Each of the 40 PD patients was matched as closely as possible to a healthy control in terms of age and pre-morbid IQ using the NART. Compared to their controls, the PD-NCI group was impaired on a single measure in two domains: working memory and memory/learning. The PD-UCI group was impaired on single measures from three different domains: executive function; speed of processing; and visuospatial ability. However, the PD-MCI group was impaired on multiple measures over five domains: executive function; problem solving; working memory; speed of processing; and visuospatial ability.

All patients, regardless of group, showed a mild deficit ($\geq$ 1 SD below the control group norm) and/or severe deficit ($\geq$ 2 SD below the control group norm) on at least one measure in one or more of the six cognitive domains. When we assessed the number of patients from each group who showed impairment on at least one of the six domains, the PD-NCI group had little evidence of severe cognitive impairments (i.e., 84.2% of the patients in this group exhibited severe deficits in $\leq$ 1 of the six cognitive domains tested). Only 21% (4/19) showed severe deficits in two or more domains. By contrast, in the PD-UCI group 77.8% (7/9) of the patients had severe impairment in 2 or more domains, and all of the patients in the PD-MCI group had severe deficits in two or more domains.

Differences for the groups of PD patients compared to their matched controls were also found in terms of functions of daily living. Whereas the PD-NCI group were comparable to their matched controls in this regard, both the PD-UCI and PD-MCI groups were considerably more impaired than their controls.

Consistent with previous research, our study found evidence for different sub-groups of PD patients based on cognitive functioning (Lewis et al., 2005). The importance of accurately defining different subgroups is amplified by the suggestion that some PD patients may be more at risk of progressing to PDD (Janvin, Larsen, Aarsland, & Hugdahl, 2006). Prevalence rates of dementia among people with PD are much higher than in the general population, approximately four to five times that of elderly individuals without PD.(Aarsland, Andersen, Larsen, Lolk, & Kragh-Sorensen, 2003).

However, the cognitive symptoms associated with the preclinical phase of PDD have yet to be fully established. Previous studies have found evidence for a range of different cognitive deficits that may best predict PDD, including attention, (Woods & Troster, 2003) inhibition(Mahieux et al., 1998), mental flexibility (Janvin, Aarsland, & Larsen, 2005), memory(Levy et al., 2002), language (Hobson & Meara, 2004), and phonemic/semantic fluency (Jacobs et al., 1995). While the range of measures previously suggested as predictive of PDD may seem diverse, the majority of them reflect what would generally be considered as executive functions, which have previously been suggested as the most common deficit in PD-MCI (Caviness et al., 2007). In this study, all patients in the PD-UCI and PD-MCI subgroup had severe deficits of visuospatial ability and all but two patients in the PD-MCI group had severe deficits in executive functioning. Many patients in the PD-MCI group also had deficits in other areas of cognitive functioning. The only area that appeared to be spared was general memory/learning.

Progression to dementia has been reported by some as being more likely in patients with longer disease duration, older age, and more severe motor symptoms

(Biggins et al., 1992; Caparros-Lefebvre, Pecheux, Petit, Duhamel, & Petit, 1995; Mahieux et al., 1998). However, this finding was not supported in our study. Indeed the subgroups were comparable on most of the demographic, clinical and motor characteristics assessed. Moreover, other research suggests that clinical and motor characteristics by themselves are not sufficient to identify patients in the pre-clinical stages of PDD (Graham & Sagar, 1999) Furthermore, longer disease duration and severe motor problems are also more likely to be associated with older patients, and older people in general are more likely to progress to dementia.

This study had a number of strengths as it used a wide range of tests across a broad range of possible domains, to determine cognitive deficits for the different groups. Also, we used a data driven approach to examine the data to avoid the difficulties of predetermined cut offs. However, a limitation of the study was the use of a cross-sectional design. The groups identified here would have to be followed longitudinally to confirm whether the patients in the PD-MCI group were indeed more likely to progress to dementia. Furthermore, the number of patients in two of the groups identified by the cluster analysis was relatively small.

It is clear from these findings that patients with PD are heterogeneous with regard to their cognitive presentation. Furthermore, the severity of cognitive deficits cannot be predicted by other clinical and demographic characteristics such as motor impairments, age, or disease duration. We identified a group of patients with severe cognitive deficits over multiple domains and with evidence of problems in daily living that may be characteristic of PDD. Longitudinal assessment of patients in this study is underway and will be essential to confirm the initial findings.

The identification of diagnostic criteria associated with PD-MCI would present an opportunity to intervene and delay the onset of more severe cognitive problems that may result in later dementia. Preliminary research indicates that, as with AD, the cognitive impairments associated with PDD may be improved with cholinesterase inhibitors without worsening motor symptoms(2003). Thus, early identification of individuals likely to develop PDD could be the basis for early intervention that could slow its development.

4.5 The Cognitive Characteristics of Pre-clinical Dementia in Parkinson's Disease

4.5.1 Abstract

The aim of this study was to track the evolution of cognitive decline in PD patients order to identify a profile of pre-clinical dementia for this group. Thirty three PD patients, divided into three sub-groups based on their initial cognitive performance, and their matched healthy controls were reassessed after a 1 year interval. At initial assessment, one group of PD patients had no cognitive impairments (PD-NCI) and one had uncertain cognitive impairments (PD-UCI). The third group had evidence severe cognitive impairments analogous to the state of pre-clinical dementia found in early Alzheimer's disease termed "Mild Cognitive Impairment". This latter group was labeled PD-MCI. These PD groups were comparable with regard to motor impairments, age and education. Patients were assessed over five domains:1) executive function; 2) problem solving; 3) working memory/attention; 4) memory, and 5) visuospatial ability. The PD groups differed on the domains of executive function, problem solving and working memory with greatest deficits being evident for the PD-MCI group. In terms of visuospatial ability, there was evidence of equivalent deficits for both the PD-UCI group and the PD-MCI group. When compared to their matched controls the PD-NCI group differed on only 1 of 15 measures tested and the PD-UCI on only two out of the 15. But the PD-MCI group on was impaired on 6/15 measures over 3 domains (executive function, working memory and problem solving). Increasing cognitive problems were also associated with decreased functioning in activities of daily living. There was clear evidence of increasing cognitive decline across the three PD groups. The PD-MCI group had evidence of global cognitive decline, possibly reflecting a stage of pre-clinical dementia.

4.5.2 Introduction

Cognitive deficits occur frequently in patients with Parkinson's disease (PD) with about 40% of patients progressing to PD with dementia (PDD)(Cummings, 1988). Severe deficits in cognition and impairment in social functioning associated with PDD often result in reduced patient autonomy and may require early rest home care resulting in both social and personal cost. Recent research suggests that cognitive decline may be effectively treated with medical interventions (Aarsland, Hutchinson, & Larsen, 2003). The possibility of delaying the onset of PDD has resulted in an increased interest in identifying the characteristics of PD patients that may be at risk for developing dementia.

A number of clinical and demographic symptoms have been associated with PDD including older age, longer disease duration, hallucinations and more severe motor symptoms (Biggins et al., 1992; Caparros-Lefebvre, Pecheux, Petit, Duhamel, & Petit, 1995; Janvin, Aarsland, Larsen, & Hugdahl, 2003; Mahieux et al., 1998). In terms of cognitive deficits, impairments in executive functions have been reported by a number of authors as a risk factor for later dementia (Azuma, Cruz, Bayles, Tomoeda, & Montgomery, 2003; Jacobs et al., 1995; Janvin, Aarsland, & Larsen, 2005; Mahieux et al., 1998; Woods & Troster, 2003). However, deficits in executive function are common in PD patients and may lack specificity to be used as a predictor of later dementia. Unfortunately, a clear cognitive profile associated with pre-clinical PDD has yet to be identified.

Previously were assessed over a broad range of cognitive domains, including executive function, problem solving, working memory/attention, speed of processing and visuospatial ability, using common neuropsychological tests (McKinlay, Grace,

Dalrymple-Alford, & Roger - In review). This information was then used in a cluster analysis to identify sub-groups of PD patients who were heterogeneous with regard to their cognitive presentation. Three groups were identified. One group of patients had no or minimal cognitive impairments (PD-NCI) on any of the domains measured. Another group had a variable pattern of mild, moderate and severe cognitive impairments and therefore labeled as uncertain cognitive impairment (PD-UCI). However, a third group was consistently impaired on most domains tested and resembled more closely the stage of Mild Cognitive Impairment (MCI) discussed in the Alzheimer's disease (AD) literature. This term has been used to describe cognitive impairments that exceed the level of impairment usually evident with normal aging, but not of sufficient severity to warrant a diagnosis of dementia. Individuals with this level of cognitive decline are more at risk of developing AD (Petersen, 2004). Therefore, the third group was labeled PD-MCI. For all groups, executive function and visuospatial ability were the two domains most likely to be impaired, with attention and general memory being relatively unimpaired. Severity of cognitive deficits was not associated motor impairments, age or disease duration (McKinlay, Grace, Dalrymple-Alford, & Roger- In review).

The aim of this current study is to follow the evolution of these previously identified groups using a selection of tests that we had found to be sensitive to cognitive impairment in PD. We also intended to compare the groups at time two in relation to their performance at time one. We expected to see a trend for decline in our PD groups over the one year period. More specifically we wanted to examine whether this trend was more noticeable in the PD-MCI group. Thirdly, we wanted to examine the performance of the three groups in terms of their ability to perform activities of daily living. According to the Diagnostic and Statistical Manual of Mental Disorders (DSM-

IV) a diagnosis of dementia requires that the deficits in cognitive performance cause significant impairment in social functioning. Therefore, would expect to see a trend towards greater impairment in social functioning across the three PD groups compared to their healthy controls.

4.5.3 Method

Participants

Participants were all recruited from a data base of PD patients and healthy controls who had agreed to participate in a longitudinal study examining cognitive deficits in PD. Participants were approached approximately one year following the first study (the minimum period of follow up was 9 months and the maximum was 16 months). Participants who had given consent (39/40 people with PD and 40/40 of the healthy controls had consented to further follow-up at the end of first phase of testing) were first contacted by phone to ascertain whether they were still willing to participate in the second study, and if willing, given details of the studies objectives. Of the 39 patients who consented to being re-contacted, 33 were available for testing at follow-up. Of the six participants that were unavailable; one was deceased; two had been hospitalized; one was out of the city during the testing period; one declined; and one was unable to be contacted. Of the people with PD that were not available for follow-up 2 came from the PD-NCI group, 1 came from the PD-UCI group and 4 came from the PD-MCI group. Parkinson's disease patients who did not participate at time two tended to be older (mean 72.1 v 64.9, t=-2.86, df 38, p<0.01 and had lower score on the Mini Mental Status Exam (mean 27.4 v 28.9 , t=2.69, df 38, p<0.02). Controls that were matches for the patients with PD, in terms of age and pre-morbid intelligence, were also contacted, two declined to participate in the second stage of the study.

Procedure

This study received approval from the Upper South B Regional Ethics Committee. Assessments were carried out at the University of Canterbury over two testing sessions, each of three hours in duration. Tests were presented in a fixed order with breaks taken as required. All patients were on antiparkinsonian medication and were tested while on optimal levels of medication.

Inclusion criteria for patients were as follows, a diagnosis of idiopathic Parkinson's disease, confirmed by a neurologist who specialised in movement disordeers, Hoehn and Yahr stage I-IV (Hoehn & Yahr, 1967); aged between 50 and 80 years; adequate or corrected hearing and vision (self report checked by examiner) and stable on PD medication. Exclusion Criteria included 1. currently involved in a therapeutic trial; 2. A history of: a) moderate or severe head injury b) stroke or other neurological impairment c) major medical illness, d) significant psychiatric illness requiring hospitalization ; e) diagnosis of a learning disability; 3) pre-morbid IQ estimated at <85 using National Adult Reading Test (NART) (Lezak, 1995);4) Currently taking medications known to have a significant effect on the Central Nervous system (other than medications prescribed for the control of PD symptoms). In addition to adequate or corrected hearing and vision (self report, checked by the examiner) and being aged between 50 to 80 years of age, the same exclusion criteria listed above also applied to the control group. Previously patients had been excluded it they had suspected dementia (Mini Mental Status Exam <25) (Folstein, Folstein, & McHugh, 1975) or signs of depression (Beck Depression Inventory-II>17 validated for detecting depression in patients with PD, (Leentjens, 2004). However, as this study

was focused on the decline of cognitive functioning over time, these exclusion criteria were not used in the follow up assessment.

Information pertinent to the inclusion/exclusion criteria used in the second phase of the study was elicited from all participants using a semi-structured interview. Written consent was obtained from participants at the start of the first testing session after the study had been explained. Participants were also asked if a person who knew them well (a "significant other") could be contacted to provide collateral information regarding their daily living activities. If the participants agreed, the significant other was contacted, the purpose of the study was explained, and consent obtained. In most cases the significant other was a spouse or other family member. In the case of control participants, information for the significant others to complete was sent home with the participant and returned at the next testing session. For PD patients, information regarding everyday activities was collected during a face-to-face interview with a significant other person. In the majority of cases, these interviews were conducted by a second interviewer during the same time period that the patient was engaged in the second testing session.

Cognitive Assessment:

A selection of tests, for which impairments had been consistently found at time one, was used to check the stability of the groupings at time two. All tests were commonly used neuropsychological measures and scored according to standard procedures. The majority of the measures used were from standardised batteries with age-adjusted norms and included the Wechsler Abbreviated Scale of Intelligence (WASI) [Mean 50, Standard deviation10] (Wechsler, 1999), Delis Kaplan Executive Function System (D-KEFS)(Delis, Kaplan, & Kramer, 2001), and the Wechsler

Memory Scale-III (WMS-III)(Wechsler, 1997) [both mean 10, standard deviation, 3]. Such norms were not available for the Reading Span task, or tests of visuospatial functioning.

The following tests were used at time two: measures of executive functioning including the Verbal Fluency test (with subtests for letter fluency, category fluency and category fluency switching) from the D-KEFS and the CLOX-I (Royall, Cordes, & Polk, 1998). The CLOX is an unstructured drawing test that has two parts; for both parts of the test a maximum score of 15 is possible indicating perfect performance. In part one the participant is given the following instruction "Draw me a clock that says 1.45. Set the hands on the face so a child could read them" (Royall, Cordes, & Polk, 1998). Drawings are rated according to CLOX-1 directions. Problem solving was assessed using the Matrix Reasoning subtest from the WASI. Digits Forward and Backward, from the WMS-III and the Daneman and Carpenter Reading Span test (Daneman & Carpenter, 1980)(scores range from 1-6) were used to assess Working memory/attention. Memory was assessed with using the Rey Osterrieth Figure recall after 3 minutes (ROF-II), Paired Associates (immediate and delayed) and the Auditory Recall Index (truncated) from the WMS-III. The Auditory Recall Index would usually include Logical Memory I&II and Paired Associates I&II with scores ranging from 0-54. However, only Paired Associates were used at this assessment period therefore, scores varied from 0-24. The truncated scores were not able to be converted into age adjusted scores. Visuospatial ability was assessed using the Judgement of Line Orientation (JLO) (Benton, Varney, & Hamsher, 1978), scores reported for the JLO are the number of correct line pairs, with possible scores ranging from 0-30, The Rey Osterrieth Figure copy task and the CLOX part two. Scoring for both parts of the Rey Osterrieth Figure as scored the same and can vary from 0-36, with higher scores

indicating more accurate performance (Spreen & Strauss, 1998). For the CLOX-II, the examiner first draws a picture of a clock face with the hands on the clock face set at 1.45. The participant is then asked to copy the examiner's drawing (Royall, Cordes, & Polk, 1998). Although speed of processing, as measured by the Stroop task from the D-KEFS, had significantly differentiated the three groups at time one, this domain was not included at time two due to the difficulty that more cognitively impaired patients had in understanding the instructions. Also, as there was no evidence of a planning deficit at time one for PD patients v controls or for the different PD groups this domain was not included at time two.

The Dementia Rating Scale (DRS-2) (Jurica 2001) was used to provide a global assessment of cognitive ability. This scale consists of 36 tasks and five subscales. The five subscales provide information on specific abilities and include: 1. Attention; 2. Initiation/Perseveration; 3. Construction ability; 4. Conceptualization; and 5. Memory. Based on normative data, raw scores from each subscale were summed to provide an overall score (ranging from 0-144 with higher scores indicating better performance). A combined scaled score adjusted for age and education was then generated using a regression formula provided in the administration manual (Jurica, 2001).

Assessment of Activities of Daily Living:

The Functional Activities Questionnaire (FAQ)(Pfeffer, Kurosaki, Harrah, Chance, & Filos, 1982) was used to assess the patients functional capacity and includes items such as, ability to prepare a balanced meal or remembering appointments. The questionnaire was completed by a significant other who rated the participants on their ability to do the 10 higher order tasks listed by ticking the box for the word or phrase that applied best using a 4 point scale (dependent = 3, requires assistance = 2, has

difficulty but does by self = 1, no difficulty = 0). A total score for the FAQ is obtained by summing the scores across the 10 items. Dependent on three or more items is recommended as a cut off indicating mild impairment in normal activities or independence (Pfeffer, Kurosaki, Harrah, Chance, & Filos, 1982).

Assessment of Dementia:

The DRS-II and the MMSE were used to screen for dementia. Patients with a MMSE score of below 25 and or a total raw DRS-II score between 120 and 130 were further assessed for dementia by a registered clinical psychologist using the Diagnostic and Statistical Manual of Mental Disorders-IV (DSM-IV) criteria. This DRS-II score has previously been validated as appropriate for PD patients (Brown et al., 1999). Two patients scored below 130, one from the PD-NCI group and the other from the PD-MCI group. Only the patient from the PD-MCI group showed evidence of possible dementia.

4.5.4 Statistical Analysis

ANOVA's were used to compare the three PD groups in terms of their clinical and demographic characteristics. Scores were then converted to z-scores based on the control mean. Student t-tests were used to compare each of the three PD groups with their matched controls on the 15 cognitive measures. Descriptive measures were then used to examine severity and frequency of impairments within each group. In order to make direct comparisons regarding performance at time one and time two, a repeated measures analysis of variance, with z-scores generated using control and SD from time one were using to generate z-scores for time one and time two. Post hoc analyses were used to test whether any differences between time one and time two were significant. ANOVA's and t-tests were also employed to test differences between the different PD

groups and their matched controls and between the three groups of PD patients on measures of daily living.

4.5.5 Results

As can be seen on Table 42, the groups were comparable on all demographic and clinical characteristics with the exception of current mental status and per-morbid intelligence.

Table 42: Comparison between the three Parkinson's disease groups identified by the cluster analysis for clinical and demographic characteristics at one year follow-up.

	PD -NCI N=17 Mean [SD]	PD-UCI N=8 Mean [SD]	PD-MCI N=8 Mean [SD]	F	*p*-level
MMSE[1]	29.24 [0.7]	29.13 [0.8]	27.50 [1.4]	7.77	<0.01
Years of Education	15.09 [3.1]	12.88 [1.9]	12.75 [0.9]	3.31	<0.10
NART[2]	115.88 [7.5]	103.38 [8.4]	100.00 [7.7]	14.11	<0.001
Age[3]	63.65 [6.5]	65.38 [7.7]	67.00 [5.6]	0.73	>0.45
UPDRS Total [4]	26.00 [10.0]	26.38 [9.7]	31.25 [6.6]	0.33	>0.30
PD Onset[5]	5.41 [3.5]	6.13 [3.0]	8.28 [7.2]	1.08	>0.35
H&Y[6]	2.23 [0.6]	2.13 [0.8]	2.63 [0.7]	0.36	>0.30
BDI-II[7]	9.41 [5.4]	9.38 [6.0]	7.62 [4.2]	0.51	<0.60

[1] Mini Mental Status Exam; [2] Premorbid intelligence estimate using the National Adult Reading Test; [3] As at time one; [4]Unified Parkinson's disease rating scale motor score; [5] Number of years since Parkinson's disease was first diagnosed as at time one; [6] Hoehn& Yahr stage; [7] Beck Depression Inventory-II.

Each PD patient had been match as closely as possible to a healthy control in terms of age and pre-morbid intelligence. Subject loss did not change the overall accuracy of the original matching in terms of age (PD-NCI v Control, t=0.69, df, 32, p>0.45; PD-UCI v Control, t=-0.24, df, 14, p>0.80; PD-MCI v Control, t=0.26, df,14,

p>0.80) or pre-morbid intelligence (PD-NCI v Control, t=0.60, df, 32, p>0.50; PD-UCI v Control, t=-0.42, df, 14, p>0.65; PD-MCI v Control, t=0.68, df, 14, p>0.50).

Comparisons between the three groups for the 15 measures are shown in Figure 11 and Table 43. Bolded p values in Table 43 indicate where significant group differences had been found at time one. Analysis of variance (ANOVA's) confirmed that there was a significant overall group difference for all measures of executive functioning and the measure of problem solving (all p<0.02). Only one measure of working memory (Digits Backward), memory (Auditory Recall Index) and Visuospatial ability (Line Orientation) discriminated between the three PD groups. Consistent with our previous findings, there was no significant difference between the groups in terms of attention as measured by digits Forward.

Table 43: Comparison between the three Parkinson's disease groups identified by the cluster analysis on tests of cognition at the one year follow-up.

	PD-NCI N=17 Mean [SD]	PD-UCI N=8 Mean[SD]	PD-MCI N=8 Mean [SD]	F	*p*-level
Executive Functioning					
Verbal Fluency sub-tests: [a]					
• Letter Fluency	13.38 [3.8]	10.00 [3.0]	7.75 [1.6]	9.01	**<0.001**
• Category Fluency	11.81 [2.8]	9.75 [3.5]	6.50 [1.1]	10.14	**<0.001**
• Category Switching	12.00 [3.3]	10.37 [3.9]	6.50 [2.9]	7.10	**<0.01**
CLOX-I	13.94 [1.7]	13.38 [1.4]	11.43 [2.3]	4.83	**<0.02**
Problem Solving					
Matrix Reasoning [b]	58.71 [7.0]	52.00 [9.6]	45.25 [10.9]	6.69	**<0.01**
Working Memory/ Attention					
Digits Forward [b]	11.12 [2.4]	10.00 [2.0]	9.88 [1.1]	1.32	>0.25
Digits Backward [b]	7.88 [2.3]	5.88 [1.7]	4.50 [1.5]	8.12	**<0.01**
Reading Span Test	1.97 [0.6]	1.94 [0.7]	1.50 [0.5]	1.84	>0.15
Memory					
Paired Associates immediate [c]	9.63 [3.3]	8.63 [2.6]	6.88 [2.2]	2.39	>0.10
Paired Associates delayed [c]	10.10 [3.2]	9.25 [3.0]	8.25 [2.5]	1.00	>0.40
Auditory Recall index [c]	23.94 [03]	24.00 [0.0]	23.38 [0.9]	4.39	**<0.05**
ROF-II	19.41 [7.0]	16.44 [7.9]	12.50 [8.8]	2.03	<0.10
Visuospatial Ability					
ROF-I	33.81 [3.3]	30.88 [4.0]	31.38 [5.2]	1.83	**>0.10**
Line Orientation	27.06 [4.2]	20.38 [4.8]	22.75 [2.1]	8.44	**<0.01**
CLOX-II	15.00 [0.0]	14.50 [0.8]	14.43 [1.0]	2.83	**<0.10**

[a]Delis Kaplan Executive Functioning System standardised scores; [b] Wechsler Abbreviated Intelligence Scale standardised scores; [c] Wechsler Memory Scale- 3rd edition, standardised scores. Bold *p* values indicate where significant differences had been evident at time one ($p<0.01$).

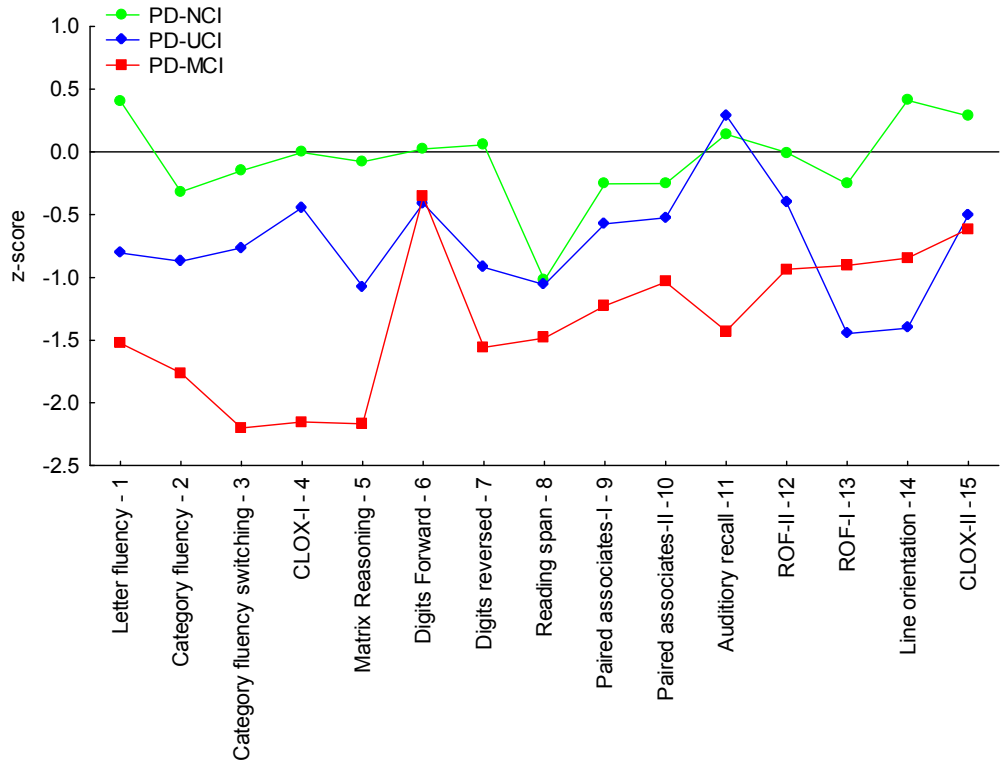


Figure 11: Comparisions between the three groups of Parkinson's disese patients on measures of cognitive functioning.

As shown on Figure 11, at the one year follow-up the three groups previously identified by the cluster analyses maintained evidence for a continuum of impairment. For the 15 cognitive measures used, a significant difference was found between PD-NCI and their matched controls for one measure of working memory, Reading span (t=3.20, *df*, 17) and for PD-UCI group compared to their matched controls one measure of verbal fluency (t=2.25, *df*, 14) and one measure of visuospatial ability, (t=2.34, *df*, 14). But the PD-MCI group were significantly different from their controls on measures of executive function (Letter Fluency, t=3.96, *df*,14; Category Fluency , t=3.90, *df*, 14, and Category Switching (t=5.01, *df*, 14), problem solving (Matrix Reasoning (t=3.62, *df*, 16), and working memory (Digits Backward, t=3.13, *df,* 14 and Reading Span t=5.02, *df*,14). No deficits were evident for any of the PD groups

compared to their matched controls for attention (Digits Forward) or Memory (Paired Associated-I & II, Auditory Recall and ROF-II). Only the PD-UCI group showed evidence of impairment in visuospatial ability (Figure 12).

Comparisons were made between scores at time one and time two using average z-scores based on time one control mean and SD. Average scores were generated using 14 of the 15 measures shown on Table 43. One measure was excluded as there was no exact comparison at time one (Auditory Recall-truncated). As can be seen on Figure 13, PD from healthy controls (F=32.73, df=1, p<0.0001), and each PD group was significantly different from their matched controls (F=6.26, df=2, p<0.01). A significant difference across the three PD groups was also evident (F=5.03, df=2, p<0.05). However, there was no significant group by time interaction (F=2.25, df=1, p>0.10).

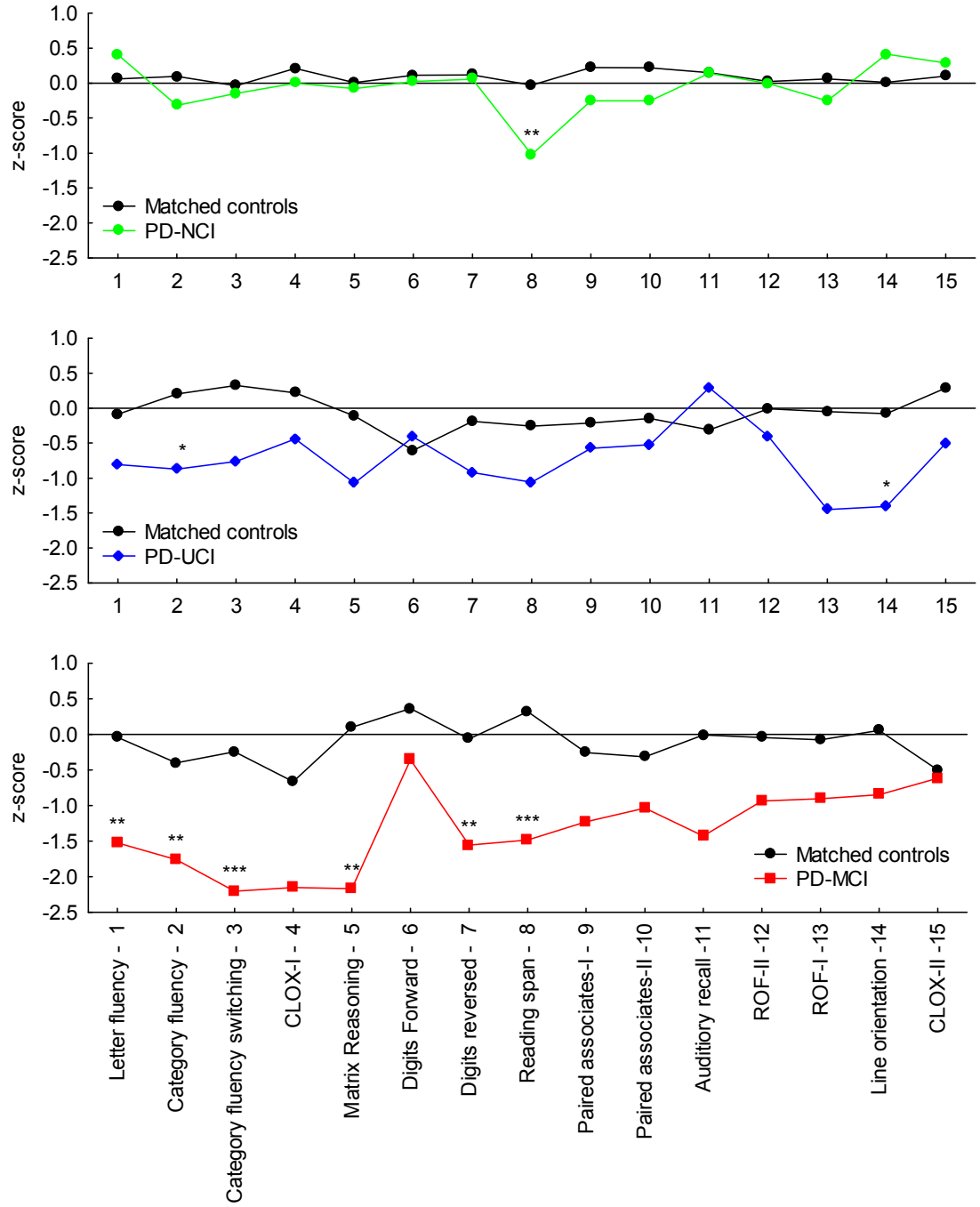


Figure 12: Comparison between Parkinson's disease patients and matched controls on a truncated set of measures of cognitive functioning at time two.

*p<0.05; ** p<0.01; ***p<0.001.

As can be seen on Figure 13, the PD-UCI patients appeared to improve over the one year follow-up period. However, post hoc analyses indicated that this change was not significant.

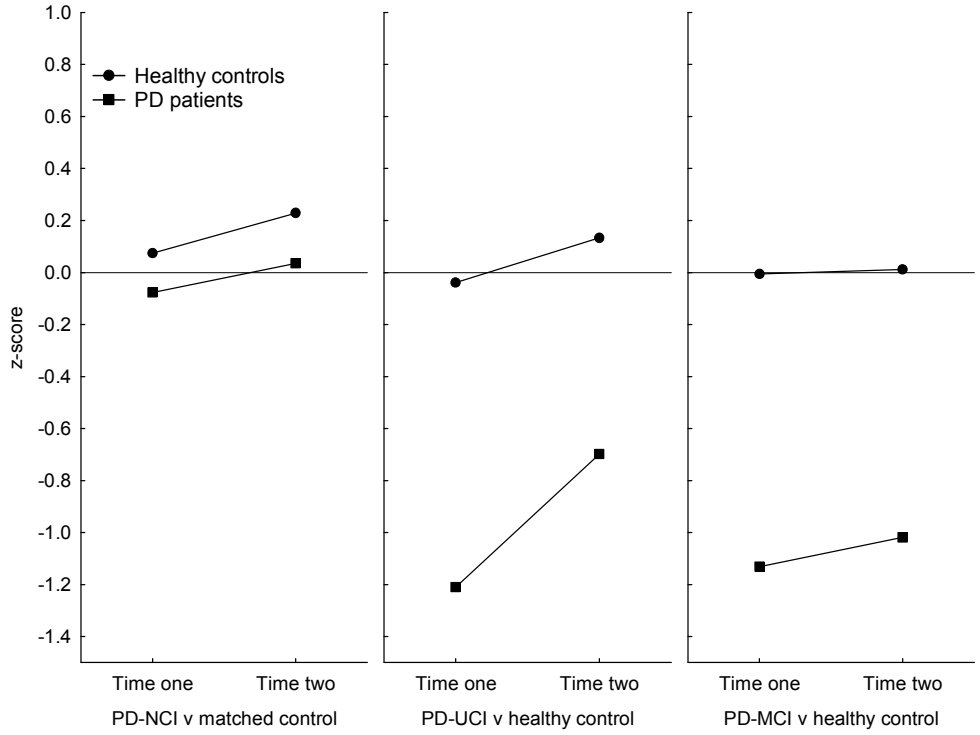


Figure 13: Comparison between PD-NCI, PD-UCI and PD-MCI and their matched controls for average z-scores at time one versus time two.
(z = 0 is mean at time one.)

As can be seen in Figure 14, PD patients performed more poorly than healthy controls on the DRS-II. There was an overall group difference for PD compared to healthy controls (F=7.63, df=1, p<0.01) and across three PD groups (F=3.62, df= 2, p<0.05). When compared to their matched controls, there was no significant difference for the PD-NCI (t=1.6, df=32, p>0.10) or the PD-UCI (t=1.3, df=14, p>0.20) group.

However, a significant difference was evident for the PD-MCI group compared to their matched control group (t=2.2, df=14, p<0.05).

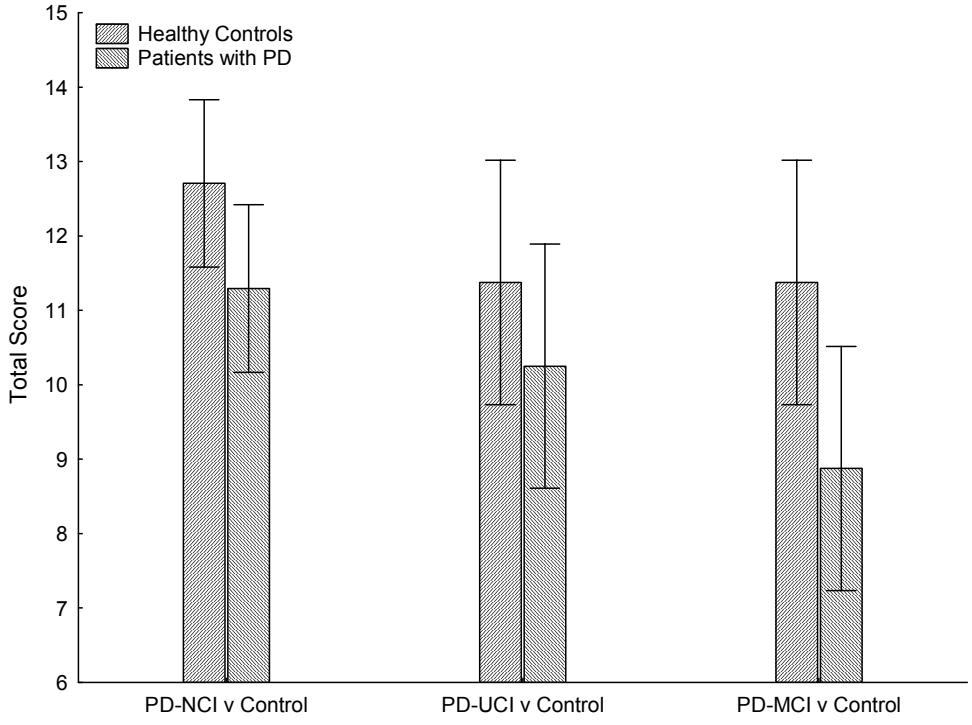


Figure 14: Comparison between Parkinson's disease patients and matched control using the Dementia Rating Scale ajusted for age and education.

As shown in Figure 15 there was an over all group difference for PD patients and healthy controls using the Functional Activities Questionnaire (F=13.2, df=1, p<0.001). Each of the PD groups were significantly different from their matched control group (PD-NCI t=-2.2, df=27, p<0.05; PD-UCI, t=-2.3, df=11, p<0.05 and PD-MCI, t=-2.2, df=13, p<0.05). However, there was no significant difference between the three PD groups (F=0.60, df=2, p<0.55).

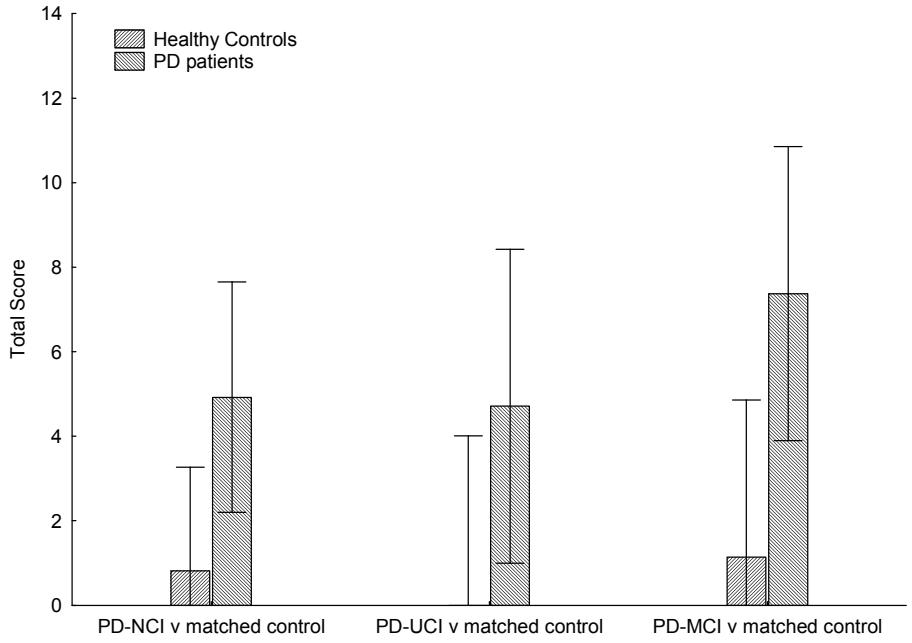
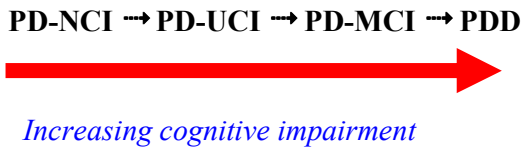


Figure 15: Comparison between Parkinson's diseae patients and matched healthy controls using the Functional Activities Questionnaire.
(PD-NCI n= 15 v matched control n=13; PD-UCI n=7 v matched control n=7; PD-MCI n= 8 v matched control n=7.)

4.5.6 Discussion

The aim of this research was to identify the profile of PD patients using previously identified groupings based on cognitive performance. The three groupings formed a continuum of cognitive impairment. At one end of the continuum was a PD group that had little or no evidence cognitive impairment (PD-NCI), at the other was a group with evidence of impairment on most domains tested (PD-MCI). A third, intermediate group had a more variable pattern of deficits showing evidence of severe impairment on some domains and no impairment on others-these were considered to have an uncertain level of cognitive impairment (PD-UCI). Based on findings from the literature regarding Alzheimer's Disease, we hypothesised that patients in the PD-MCI

would form a group with cognitive deficits more severe than those generally associated with PD or normal aging, and these patients would be more likely to show evidence of dementia (PDD) over time as depicted by the illustration below.



At the one year follow-up reported here, we used a set of tests from 5 cognitive domains (executive function, problem solving, working memory/attention, memory and visuospatial ability) that we previously had found to differentiate the PD groups. Significant differences between the three PD groups on measures of executive function, problem solving, working memory and general memory were still evident at the 1 year follow-up. Impairments in each of these domains were greatest for the PD-MCI group. In terms of visuospatial ability, there was evidence of equivalent deficits for both the PD-UCI group and the PD-MCI group. There were no differences between the groups for the measure of attention. These findings were consistent with our time one results.

As the groups differed in terms pre-morbid intelligence we also compared them to controls that were matched in terms of age and pre-morbid intelligence. There was clear evidence of increasing impairment for the three groups, while the PD-NCI group differed from their matched controls on only 1 of 15 measures tested and the PD-UCI on only two out of the 15, the PD-MCI group on was impaired on 6/15 measures (3 out of the 5 cognitive domains tested). There was consistent evidence of deficits in verbal fluency which has previously been suggested as an indicator of more global cognitive impairment and possibly predicative of later dementia(Jacobs et al., 1995). However,

only one patient from the PD-MCI group had symptoms consistent with the DSM-IV criteria for possible dementia at the one year follow-up. This finding may be conservative as 33% (4/12) of the PD-MCI group were not available for testing at time two and these patients tended to be older and perform more poorly on the MMSE.

When performance at time one was compared with that at time two, using z-scores based on the time one control mean and standard deviation, there were significant differences between the PD patients and healthy controls. Each PD group was significantly different from their matched controls and a significant difference across the three PD groups was also evident. However, there was no evidence of increasing deficits across time for any of the groups. Indeed while the PD-NCI and PD-MCI group remained relatively stable over the one year follow-up the PD-UCI group appeared to improve. This finding may in part be explained by the fact that only tests that significantly discriminated between the groups were used at time two. For example, the PD-UCI group tended to do better than the other two PD groups on tests of memory and when this effect was removed from the overall time one scores the PD-UCI groups overall score dropped.

One question was whether the cognitive deficits detected would have an impact on the ability of the individual to function in every day living. This is important as a diagnosis of dementia requires evidence of deficits in social or occupational functioning (DSM-IV). In terms of functioning in activities of daily living PD patients performed more poorly than controls and there was evidence of increased problems for the PD-MCI group. The increased difficulties with every day functioning that was apparent for the PD groups is consistent with our hypothesis that the PD-MCI group represents a level of cognitive impairment that is indicative of pre-clinical dementia. It could be

questioned whether the individuals in the PD-MCI group are simply more physically impaired. However, the three PD groups were comparable with regard to motor impairments as measured by the UPDRS or H&Y stage.

There is little information regarding the possible profile of cognitive deficits that may reflect pre-clinical dementia in PD with most research focusing on which deficit is most predictive of dementia. However, deficits in executive function have previously been associated with increasing decline in cognitive performance and a potential indicator of pre-clinical dementia (Jacobs et al., 1995; Janvin, Aarsland, & Larsen, 2005; Montse, Pere, Carme, Francesc, & Eduardo, 2001). In this current study there was little evidence of memory problems for any of the three PD groups. While this finding is consistent with some research (Ross, 1996; Woods & Troster, 2003) the opposite finding has also been reported (Levy et al., 2002). This inconsistency likely reflects different characteristics of patient groups and the variety of tests that have been used to assess these deficits. We also found a variable pattern of visuospatial deficits. Visuospatial deficits have been found to differentiate PD patients from healthy controls but have not been reported as predictive of pre-clinical dementia(Levy et al., 2002; Mahieux et al., 1998). Consistent with previous research we found no evidence of deficits in attention (Mayeux et al., 1995; Woods & Troster, 2003). Therefore, from this study and the current literature the cognitive profile associated with pre-clinical dementia appears to include executive function, problem solving and working memory deficits, with more variable outcomes associated with and visuospatial abilities. Unlike Alzheimer's disease general memory problems do not appear to be associated with pre-clinical dementia in PD. Moreover, attentional and planning skills appear to remain intact (Mayeux et al., 1995; McKinlay, Grace, Dalrymple-Alford, & Roger; Woods & Troster, 2003).

This study had a number of strengths. A longitudinal design was used to investigate the cognitive profile of pre-clinical dementia in PD. Further, a healthy control group was used to compare the PD groups and the study also used a broad selection of tests to assess any deficits. We also investigated how deficits in cognitive functioning related to functional activities of daily living. However, the study had a number of weaknesses; some of the more poorly performing patients were not available at this 1 year follow-up, and the number of patients in each of the sub-groups was less than ideal. However, despite the loss of participants the overall pattern of deficits found at time one were consistent with the findings at time two.

Conclusions

The concept of PD-MCI could provide an important avenue for understanding cognitive deficits in PD. Moreover, the concept of PD-MCI presents an opportunity to intervene and delay the onset of more severe cognitive problems that may result in later dementia. However, to effectively intervene, a profile of both spared and impaired abilities needs to be identified. The cognitive profile of the most impaired patients, those who may represent a pre-clinical dementia group, included deficits in executive function, problem solving and working memory. There were also spared functions including attention and most aspects of memory. Decreased functioning in activities of daily living was also associated with increasing cognitive problems. Further follow-up of this group is necessary to monitor how the cognitive profile of these groups will evolve.

4.6 Identification of a Discrete Battery of Tests to Detect Patients in Stage of Pre-Clinical Dementia (PD-MCI)

4.6.1 Overview

The idea of MCI provides a useful way of conceptualising cognitive decline in PD and may be valuable in guiding appropriate treatment interventions (see Figure 16 for a suggested decision tree for differential diagnosis of PD-MCI). Unfortunately, there is currently no consensus regarding the cognitive profile that is indicative of preclinical dementia in PD or for the tests that should be used evaluate potential cognitive and neuropsychiatric problems. This dearth of information limits the use of decisions trees, such as the one suggested below, to assist clinical judgement.

Therefore, one aim of this study that had an immediate practical application was to develop a discrete group of non-invasive tests for use in clinical settings. Achieving this objective required the identification of the cognitive profile specific to PD. Based on this profile the most sensitive and appropriate combination of measures could be selected for use in detecting the onset of cognitive decline (taking into account the possible neuropsychiatric problems that might accompany this disorder) in patients with PD.

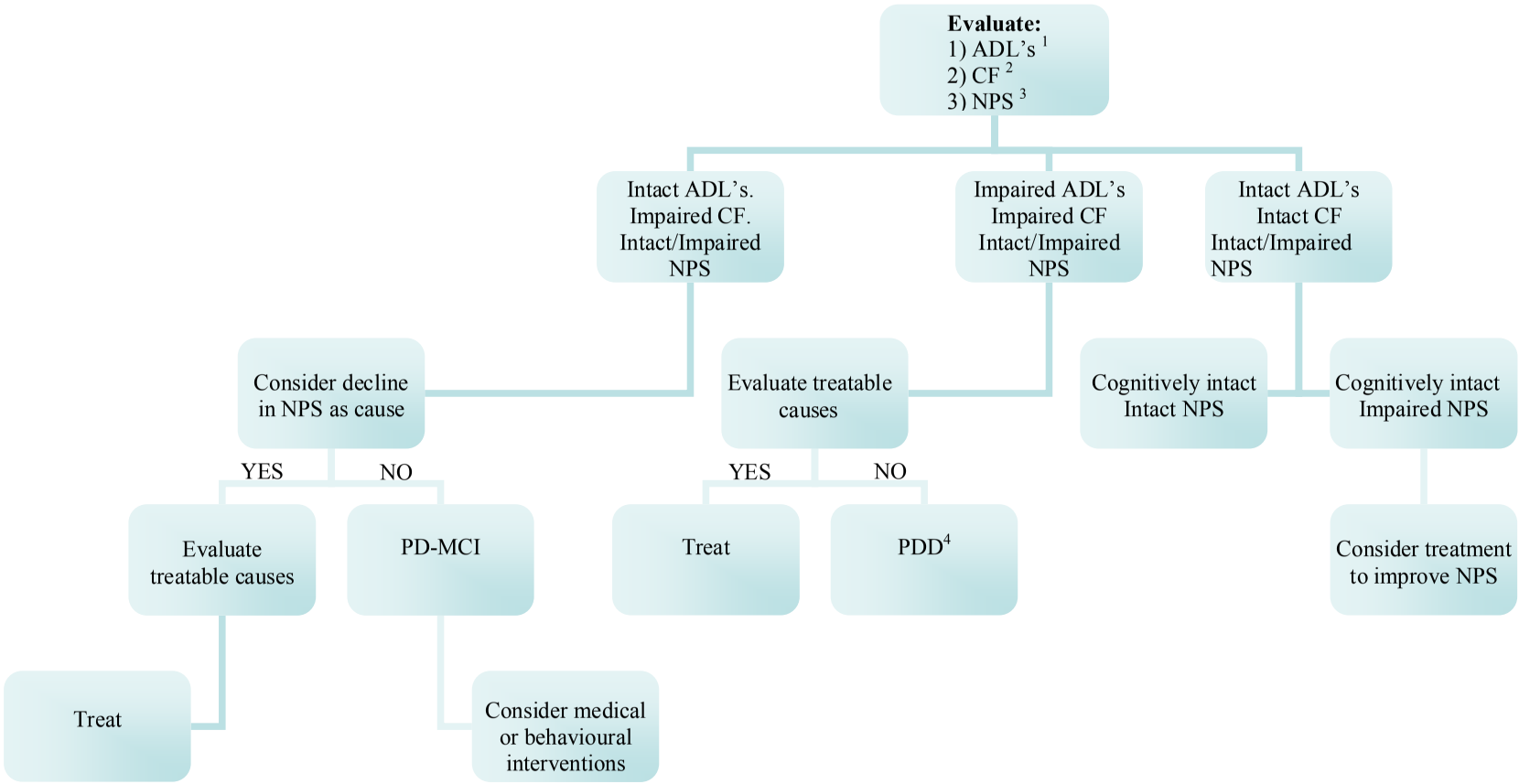


Figure 16: Decision Tree for differential diagnosis of Parkinson's disease with mild cognitive impairment (PD-MCI).

Activities of Daily Living; [2]Cognitive Function; [3]Neuropsychiatric Status; [4]Parkinson's Disease with Dementia.

4.6.2 Process for identification of cognitive profile

There were a number of steps undertaken in this project to detect the cognitive profile in PD and the measures that might be most sensitive to cognitive impairments and decline (see Figure 17 for overview) these included:

Review of Literature:

- Firstly, a comprehensive search and critical review of the literature published between 1980 and 2006 was performed to assemble the most relevant evidence on cognitive performance for patients with PD. The primary sources of literature were Medline and PsycINFO. Citations were screened for relevance to cognitive deficit associated with PD. Additional studies were found by hand-searching references lists for relevant articles.

- The systematic process of review identified over one hundred and twenty five tests that had previously been used to assess cognitive performance in patients with PD[4]. Many of these tests were conceptually similar, so the most appropriate of these were used[5]. As the proposed test battery was intended to be used with patients longitudinally to track individual performance, tests which placed high demands on fine motor skills or speeded performance were also eliminated.

[4] One test of particular note, the Wisconsin Card Sorting test has been used extensively with PD patients. However, it has a lengthy administration time therefore, this test was replaced with a conceptually similar test that had a shorter administration time (ID/ED shift from the CANTAB).
[5] Some tests had been developed specifically for a particular experimental design and did not have wider applicability and therefore were not included.

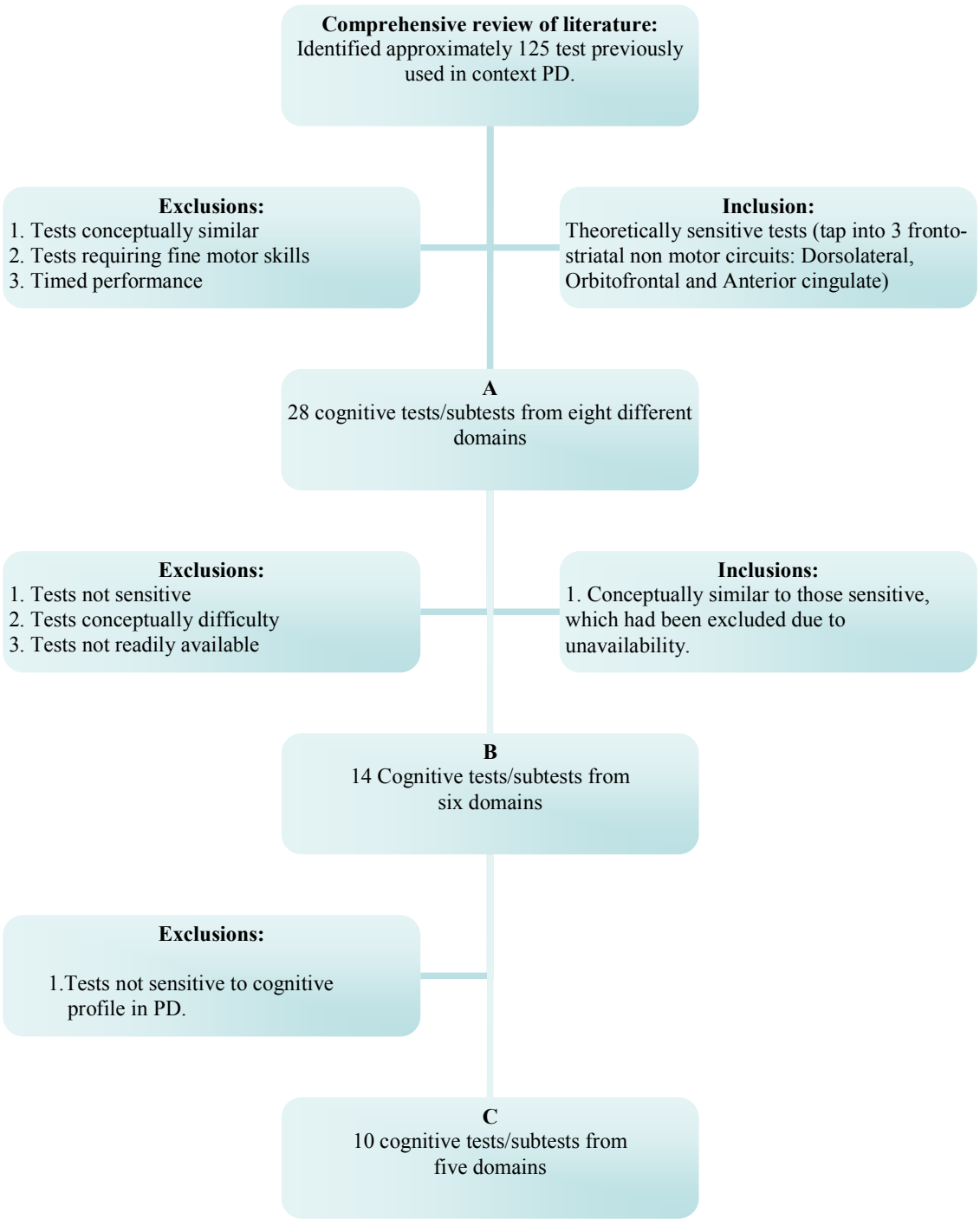


Figure 17: Overview of test selection based on findings from the PhD reseach.

- The selection of tests was further refined based on current theoretical understanding of cortical and sub-cortical changes associated with PD which could be expected to impact on cognitive and neuropsychiatric functioning.

4.6.3 Step A - 28 cognitive tests/subtests from eight different domains

- From the tests identified, 28 tests over 8 different domains (executive function, planning, problem solving, working memory, attention, speed of processing, memory/learning, visuospatial ability) were selected for further evaluation based on the criteria outlined above (see Table 44 below).

- Tests that did not differentiate between group or within group differences were excluded at this point. There were some exceptions to this rule and these are outlined below.

- Of the selected tests, 13 over five domains (executive functioning, problem solving, working memory, speed of processing, visuospatial ability) differentiated PD v healthy controls (see numbered tests on left hand of Table 43) eight of these also differentiated a continuum of cognitive decline for different sub-groups of patients (see numbered tests on right hand side of Table 43).

Table 44: Cognitive tests selected for initial analysis.

Distinguished healthy control v PD	Tests	Distinguished sub-groups of PD patients
	Executive Functioning/Planning	
	Verbal Fluency sub-tests: [a]	
	• Letter Fluency	1
1	• Category Fluency	
2	• Category Switching	**2**
3	CLOX-I	**3**
	Key Search [b]	
	Zoo Map [b]	
	Color-Word Interference sub-tests:[a]	
4	• Inhibition	**4**
5	• Switching	**5**
	ID/ED- Phases completed [c]	
	Problem solving	
	Sorting sub-tests: [a]	
	• Card sorting	
	• Card sorting description	6
6	Matrix reasoning [d]	**7**
7	Stockings of Cambridge [c (1)]	**8**
	Tower Test [a (2)]	
	Working Memory/ Attention	
	Digits Forward [e]	
	Digits Backward [e]	
	Letter number sequencing [e]	
8	Reading Span Test	
9	Spatial Span [c]	**9**
	Speed of Processing	
	Verbal Fluency Test: [a]	
10	• Word naming	
11	• Color naming	**10**
	Memory/Learning	
	Logical memory immediate [e]	
	Logical memory delayed [e]	
	Paired Associates immediate [e]	
	Paired Associates delayed [e]	
	Auditory Recall index [e]	
	ROF-II&III	
	Visuospatial ability	
12	ROF-I	**11**
	Line Orientation	12
13	CLOX-II	**13**

[(1)]Number of towers completed in minimum moves; [a]Delis Kaplan Executive Functioning System standardised scores; [b] Behavioural Assessment of the Dysexecutive Syndrome profile scores;[c] Cambridge Neuropsychological Test Automated Battery;[d] Wechsler Abbreviated Intelligence Scale standardised scores; [e] Wechsler Memory Scale- 3rd edition, standardised scores. Bolded numbers indicate tests able to discriminate between PD v Healthy controls and sub-groups of PD patients.

4.6.4 Step B - 14 cognitive tests/subtests from six domains

- Using the information gained from both the between and within group comparisons and prior to commencement of the one year follow-up, a number of criteria were imposed to ensure that the battery of tests developed would be of use to a wide range of clinicians:

    - Tests were required to be readily available for use by clinicians. All CANTAB tasks were eliminated on this criterion (ID/ED shift, Stockings of Cambridge, Spatial Span Test).

    - Tests that posed problems for patients in terms of fine movements being required were excluded (ROF I, II and II, CLOX were eliminated on this criterion).

    - Tests that were conceptually difficult were eliminated (The Stroop task proved to be impossible for many of the people in the MCI group).

This latter question was most important as it was intended that these tests would be useful not only for identifying patients who were more cognitively impaired, but also for following patients longitudinally as they became increasingly more impaired and demonstrated symptoms consistent with dementia.

This process of elimination left four out of the original tests (Letter Fluency, Category Switching, Matrix Reasoning and Line Orientation). Two measures that were excluded require special mention here these were the Stoop test and the Rey Osterrieth Figure Test.

The Stoop test was excluded because more impaired patients found this task difficult. Further, a small number of patients in the early stages of dementia who had been tested in the course of this study were unable to complete the Stroop task. Therefore, the Stroop test was considered unsuitable for the purposes of this project as it was intended to follow patients long-term and to specifically include dementia groups to test the sensitivity and specificity of any identified test battery.

The Rey Osterrieth Figure was found to be an excellent test of visuospatial ability and potentially of planning ability (this hypothesis is still being investigated). Unfortunately, the task required a degree of motor control and some patients found it impossible to complete; for this reason it was also excluded.

Five other tests were retained for the following reasons:

- Category Fluency as this is a necessary step prior to Category Fluency Switching, which had been found to be sensitive to cognitive decline in PD.

- Paired Associates I&II was retained as a measure of memory ability. Although memory was unimpaired in PD patients, regardless of the their cognitive status, it was expected that as a quick and easy to administer memory/learning task, Paired Associates (or an equivalent list learning task such as the Rey Auditory Verbal Learning Test) would be useful for differentiating patients with PD-MCI from other dementias for which memory is a core feature.

- Digits Forward, and Backward were included as simple measures of attention which could be expected to be unimpaired for patients with PD without dementia.

Table 45: Selection of tests suggested as sensitive for detecting the cognitive profile of Parkinson's disease patients.

Tests time one	Tests time two
Tests of Executive function/Verbal fluency [a]	**Tests of Verbal Fluency** [a]
• Letter Fluency	• Letter Fluency
• Category Fluency	• Category Fluency
• Category Switching	• Category Switching
General Memory/Learning	**General Memory/Learning**
Paired Associates I&II	Paired Associates I&II
Tests of Working Memory /Attention	**Tests of Working Memory /Attention**
Digits Forward	Digits Forward
Digits Backward	Digits Backward
	DOT-R
Problem solving	***Problem solving***
Matrix Reasoning [b]	Matrix Reasoning [b]
	Tower task
Visuospatial ability	***Visuospatial ability***
Line Orientation	Line Orientation
	VOSP Letter Recognition
	VOSP Object Recognition

[a]Delis Kaplan Executive Functioning System standardised scores; [b] Wechsler Abbreviated Intelligence Scale standardised scores;

At the one year follow-up (time two), tests conceptually similar to those found to be sensitive at time one, but which had failed to meet the inclusion criteria for time two, were added these included:

- The VOSP Letter and Object Recognition as a measure of visuospatial ability that did not involve motor skills to replace ROF.

- The DOT-R was included as a measure of working memory performance. Working memory had been found to be impaired at time one, but the most sensitive test for working memory performance was part of the CANTAB battery. Tests from this battery were excluded as these are not in general use with clinicians.

- A computerised version of the Tower of London task was added. The CANTAB version had been found to be a sensitive measure of problem solving ability at time one but was eliminated at time two for the reasons outlined above.

Initial findings indicated that the DOT-R, Tower of London task and VOSP recognition task were able to significantly differentiate the groups and were therefore added to the final test selection.

4.6.5 Step C - 10 cognitive tests/subtests from five domains

The final selection of tests was based on measures from time one and two that were most sensitive to cognitive decline in PD and met all the criteria outlined at step A and B. In addition to the cognitive measures outlined above, tests appropriate for detecting neuropsychiatric problems were added (see Table 46).

To this suggested test battery, measures suitable for gathering collateral information were also added. The reason for this was twofold. Firstly, given the previous findings it seemed pertinent to gather information regarding significant-other distress. Moreover, information from an independent source was sought regarding

any deterioration in the ability of the PD patient to perform ADL's. Reliable information about the patients ability to complete ADLs is essential in order to differentiate those patients suffering from PD-MCI from those already in the early stages of dementia.

Table 46: The final selection of tests for assessing the cognitive profile of patients with Parkinson's disease without dementia**.**

Final Test Selection
Initial Screening /Background tests
Beck Depression Inventory (BDI-II)
Apathy Scale
Fatigue Scale
Modified Hoehn and Yahr
Unified Parkinson's disease Rating Scale (UPDRS)
Neuropsychiatric Inventory (NPI)
The Modified MMSE (3MS)
Tests of Verbal Fluency
Category Fluency
Letter Fluency
General Memory
Paired Associates I&II
Problem Solving
Matrix Reasoning (WASI)
Tower Task
Tests of Working Memory/Attention
Digits Forward
Digits Backward
Digit Ordering Test
Visuoperceptual
Judgement of Line Orientation
VOSP

4.6.6 Conclusion

The suggested test battery would provide comprehensive information regarding current cognitive and neuropsychiatric and motor status and is sufficiently brief to incorporate as part of a routine follow-up procedure. A number of the neuropsychiatric measures (BDI-II, Fatigue Scale, Apathy Scale) are suitable for

patients to complete in the waiting room prior to any consultation with their neurologist.

It is acknowledged that any set of tests suggested here are preliminary only. Further confirmation of these tests would be required i.e., in terms of their sensitivity (further evaluation with new groups of PD patients) and specificity (evaluation of the final test selection with other patient groups such as Huntington's disease, Alzheimer's dementia etc). Other confirmatory methods which identified structural changes in patients e.g. fMRI/MRI, EEG and eye-movements would also be useful for determining not only whether the suggested battery of tests were accurate but also further illuminating the cause of cognitive and neuropsychiatric problems in patients with PD.

Chapter 5 – Deficits in planning in Parkinson's disease

Abbreviations used in the text Chapter Five

1) **ANCOVAs** = Analyses of covariance; 2) **ANOVA** = analysis of variance; 3) **BDI-II** = Beck Depression Inventory; 4) **CANTAB** = Cambridge Neuropsychological Test Automated Battery; 5) **CANTAB-TOL** = Cambridge Neuropsychological Test Automated Battery - Tower subtest; 6) **D-KEFS** = Delis Kaplan Executive Function System; 7) **D-KEFS-TOH** = Delis Kaplan Executive Function System-Tower of Hanoi subtest; 8) **DRS-II** = Dementia Rating Scale-II; 9) **DSM-IV** = Diagnostic and Statistical Manual Fourth Edition; 10) **H&Y =** Hoehn and Yahr Staging Scale; 11) **MMSE =** Mini Mental Status Exam; 12) **NART** = National Adult Reading test; 13) **PD** = Parkinson's disease; 14) **TOH** = Tower of Hanoi 15) **TOL** = Tower of London; 16) **TOL** = Tower of London; 17) **UPDRS** = Unified Parkinson's disease Rating Scale.

5.1 Overview

Planning deficits have been associated with cognitive decline in Parkinson's disease (PD). However, in the initial analysis which measured cognitive performance for individuals with PD, as outlined in chapter 4, deficits in planning performance were found to be inconsistent. Therefore, to more fully complete objective 1, which was to develop a cognitive profile for PD patients, we examined planning ability in more depth.

Planning refers to the ability to look ahead through a series of possible steps, some of which may be counterintuitive, to reach a desired goal. The ability to plan is an essential part of daily living, and difficulties with this skill may impact on an individual's autonomy. Planning deficits in PD have been previously reported to be evident, even in the early stages of the disease process (Cools, Stefanova, Barker, Robbins, & Owen, 2002; Culbertson, Moberg, Duda, Stern, & Weintraub, 2004; Morris et al., 1988; Owen et al., 1992). The most common tasks used to measure planning ability in PD are the Tower of London (TOL) (Shallice, 1982) and the Tower of Hanoi (TOH).

5.1.1 Difficulty with research in this area

There are two main areas of difficulty with this area of research. Firstly, the literature is inconsistent with regard to the presence or exact nature of any planning deficits in PD, possibly reflecting the variation of TOL and TOH tasks used. Further, the TOL and TOH have been used interchangeably with PD patients, despite the fact that there is currently no evidence regarding the relative sensitivity of these two tower tasks.

Another area of difficulty relates to the complexity of different tower problems. In the PD literature little attention has been paid to the selection of problems sets. However, recent research has placed particular importance on the selection of tower problems as it has been suggested that different aspects of individual problem may increase or decrease the level of task complexity, and therefore planning demands (Berg & Byrd, 2002; Kaller, Unterrainer, Rahm, & Halsband, 2004; Ward & Allport, 1997).

5.2 Current Research

5.2.1 Manuscript 1 – Two Tower Tasks

The first manuscript in this chapter was designed to investigate the relative sensitivity of two widely and interchangeably used measures, the TOL and the TOH, for the clinical assessment of planning deficits in PD. It was found that patients were impaired on the measure of the TOL but not on the TOH. Further investigation revealed that only a very small percentage of variance between the two tasks was shared. On further analysis it was clear that the two tasks were not interchangeable and relied on different cognitive processes. While performance on the TOL was dependent on inhibition and spatial working memory, performance on the TOH was dependent on intact spatial working memory.

It was concluded that the lack of consistency in the findings between the two tower tasks could be related to a number of issues including:

1. The actual differences in the tower structures.
2. Insufficient attention to the difficulty of the problem set.
3. Variation in how performance is measured.

Therefore, a study was designed to examine the effects these issues.

5.2.2 Manuscript 2 – Problem Structure

The second manuscript was designed to examine assess planning in PD patients using a computerised version the TOL task and a problem set that systematically manipulated the problem complexity. Subtle aspects of the TOL task were hypothesised to impact on performance. These aspects include:

1. Sub-goals required
2. Search depth
3. Sub optimal alternatives
4. Counter intuitive moves
5. Start position
6. Goal position
7. Nested problems

At the most basic level, the number of moves can be considered an indicator of problem difficulty. However, two problems may have the same number of moves but differ with respect to the number of alternative moves available. This was outlined in the recent work by Berg and Byrd (2002) in their description of the "problem space" associated with the Tower of London Task. The problem space defined by Berg and Byrd (2002) is the graphic representation of the moves possible under the rules of the task. As can be seen in Figure 18, adapted from the work of Berg and Byrd (2002), for each segment of the circle there are 6 possible ball positions.

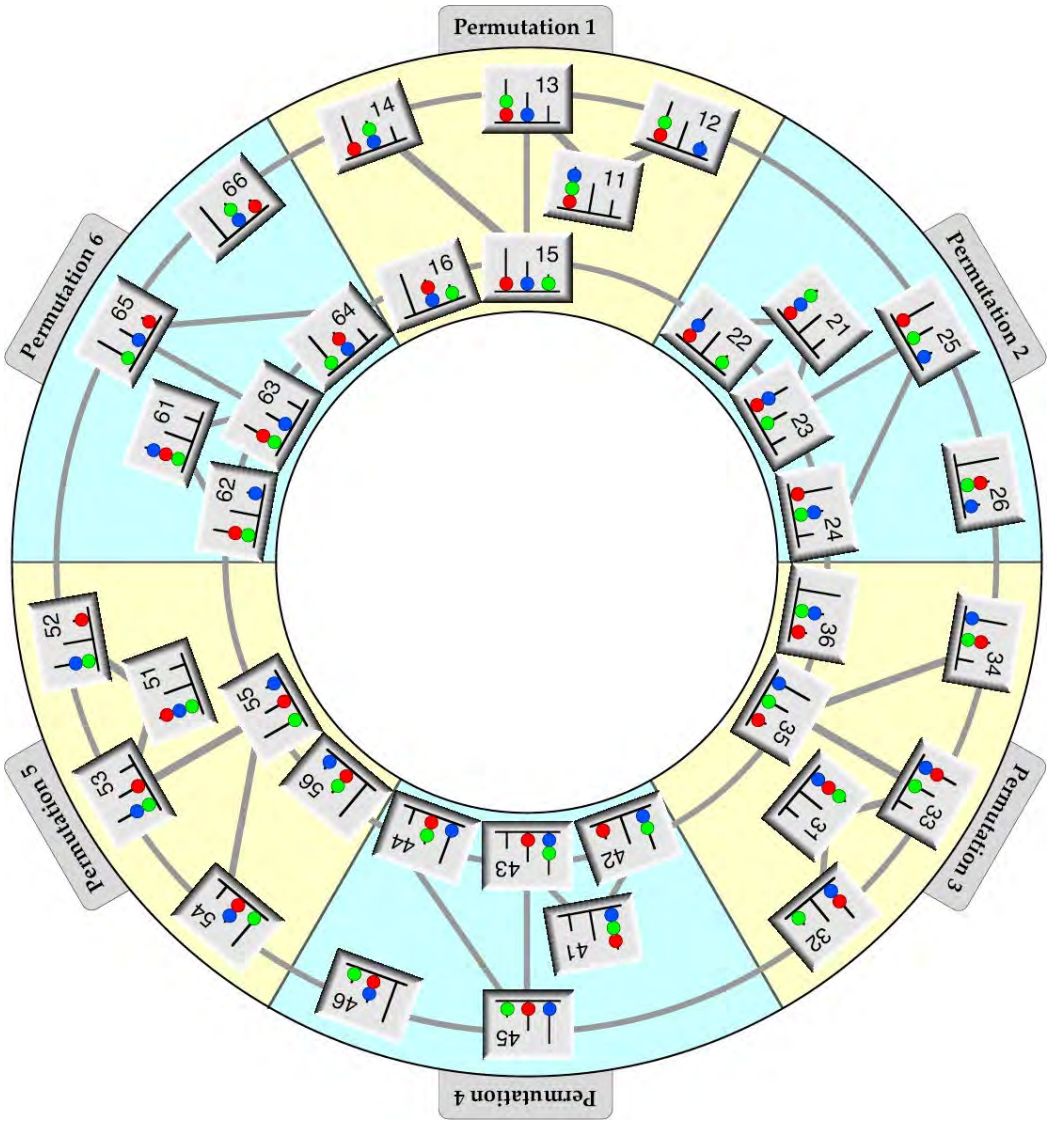


Figure 18: Problem space for the Tower of London. The various arrangements of balls in each of the 6 sections are identical, only the order of ball colors change. Adapted from Berg W.K. & Byrd D.L. (2002).

Each of the segments on the circle are the same in that they have an identical 6 possible ball positions, but differ in the arrangements of the ball colors (Berg & Byrd, 2002). There are 210 spatially unique problems for each permutation in the type of TOL task represented in Figure 18, ranging from 1-8 move problems, giving a total of 1260 possible unique problem sets (see Berg & Byrd, 2002 for a complete discussion regarding the problem space). With this graphical representation of the tower task it is easy to see that the difficulty of a particular problem may be influenced by more than just the number of moves required for its solution. For example, problems with the same number of moves may have a different 'search depth' or sub-goal pattern. A sub-goal refers to moves that are essential to the solution of a given problem, but do not place a ball into its goal position (Ward & Allport, 1997). The search depth is defined as the number of sub-goal moves before the first ball can be moved into a goal space. A longer search depth is considered to increase the difficulty of the problem as it requires more moves to be held in mind prior to being able to place the first ball in its goal position. Not only may a problem vary according to the number of paths available for achieving an optimal solution, but there may also be 'sub-optimal alternatives'. Sub-optimal alternatives refer to problems with one or more paths which take more than the minimum number of moves, but allow the first ball to be placed into its goal position within a number of moves equal to the optimal solution.

Further, the presence and number of 'counter-intuitive moves' increases complexity. Counter-intuitive moves are moves that do not lead directly to the end goal and in some cases may require a ball to first be removed from its goal state in order to perform the optimal solution. Start position and finish positions may affect

the individuals' performance. For example, in the flat start position, where there is one ball on each peg, there is no obvious first move. In contrast, a tower start position where all three balls on the tallest peg, the ordering of moves to obtain the finish position is more obvious (Berg & Byrd, 2002). Further, the latter has only two possible start moves while the former has four (Berg & Byrd, 2002). Moreover, a flat finish position provides an unclear final sequence, whereas a tower end gives a clear ordering for the sequence of final moves.

The importance of the finish position or 'goal hierarchy' has been discussed in some depth by Kaller et al., (2004). These authors suggest that a tower end position can be considered 'unambiguous' in relation to the final moves required, whereas a flat goal position can be considered 'totally ambiguous'. A goal position in between these two extremes may be considered 'partially ambiguous'. Finally, problems may be 'nested', referring to the situation where the optimal path for the first problem is contained entirely in the second. The second problem differs only with regard to the additional moves at the start or finish.

Results from our study indicated that number of moves alone could not be considered an accurate indicator of problem difficulty. Instead planning performance was influenced by more subtle aspects of problems structure, including subgoaling patters and goal hierarchy. Indeed, planning in PD patients was not impaired in general but only affected when the information provided by the problem states was ambiguous concerning the sequential order of subgoals. However, patients with PD were more likely to find problems with increased search depth more difficult than healthy controls.

5.3 Planning Deficits in Parkinson's Disease: A Comparison of Two Tower Task .

(*In review Journal of Clinical and Experimental Neuropsychology*)

5.3.1 Abstract

Variations of the Tower of Hanoi (TOH) and Shallice's Tower of London (TOL) have frequently been used to assess planning ability in patients with Parkinson's disease (PD). However, there is currently no evidence regarding the relative sensitivity of these two tower tasks with PD patients despite the fact that they are often regarded as interchangeable. Forty patients with PD met the criteria for this study. Each patient was individually matched to a healthy control in terms of age, sex and pre-morbid intelligence. Planning ability was assessed using the CANTAB-TOL task and the D-KEFS-TOH. To assess the relative contribution of different cognitive processes, participants also completed tests of working memory and inhibition. The PD group was impaired on the CANTAB-TOL but not the D-KEFS-TOH. Further, only 7%-24% of the variance between the two tasks was shared, suggesting that different cognitive processes were required for the tasks. Regression analysis revealed that performance on the CANTAB-TOL was dependent on inhibition and spatial working memory, whereas performance on the D-KEFS-TOH was dependent on spatial working memory only. The CANTAB- TOL and D-KEFS-TOH are not equally sensitive at detecting planning deficits in PD patients and should not be considered interchangeable measures of planning ability in clinical populations.

5.3.2 Introduction

Variations of the Tower of Hanoi puzzle (TOH) and Tower of London task (TOL) have been employed to assess planning ability for patients with a variety of disorders including Parkinson's disease (PD). As Welsh, Satterlee-Cartmell and Stein (1999) have pointed out, these two tasks are generally considered to be interchangeable as they purport to measure the same cognitive processes including planning. The ability to plan is an executive function in which the prefrontal cortex has pre-eminence. Because fronto-striatal degeneration is known to occur during PD, planning deficits are a distinct possibility in patients with this disorder. However, results of research that has examined planning deficits in PD patients are mixed, which may in part be due to the different versions of tasks that have been used to assess this skill.

Multiple variations of tower tasks have been used to assess planning in PD (Culbertson, Moberg, Duda, Stern, & Weintraub, 2004; Leiguarda et al., 1997; Morris et al., 1988; Owen et al., 1992; Saint-Cyr, Taylor, & Lange, 1988). For example, Culbertson et al. (2004) reported that a group of 65 PD patients (mean Hoehn & Yahr = 2.27) performed significantly worse, compared to controls, in terms of average total moves and rule and time violations. This study used the Tower of London-Drexel which is similar in construction to Shallice's TOL task (Shallice, 1982). However, Morris et al. (1988) previously reported no difference in the average number of moves taken by his participants to complete the tower problems, although the PD patients took longer to think about or plan the solution. The tower task used by Morris et al. (1988) was a computer variation of the TOL task, but used colored rectangular blocks instead of balls. Their results were supported by Saint-Cyr et al. (1988) who reported

that non-medicated PD patients with mild symptoms showed no impairment in problem solving accuracy using a three-disk version of the Tower of Toronto (a variation of the TOH task). Finally, Owen et al. (1992) examined outcomes for three sub-groups of PD patients, divided according to disease stage - early non medicated, mild to moderate stage medicated, and late stage medicated. Owen et al. reported that PD patients spent longer planning solutions compared to controls. Further, increased errors in execution of solutions were evident for patients in the later stages of the disease. Owen et al. used a computerized tower task from the Cambridge Neuropsychological Test Automated Battery (CANTAB-TOL). The CANTAB-TOL consists of two sets of three colored balls, one in the top half of the screen and the other in the bottom half, that hang in pockets similar to snooker balls. The participant is asked to make the arrangement of the colored balls in the bottom half of the screen match that in the top half using the minimum number of moves.

Overall, results of studies which have assessed planning deficits in PD patients are inconsistent. While variations in disease severity and medications may in part account for some of these findings, the lack of comparability between the different versions of tower tasks that have been used to assess planning in PD may also have contributed.

The present study compared performance of a group of PD patients with matched controls to investigate the comparability of two versions of the tower task for assessing potential planning deficits in PD patients. To this end, tower tasks from two well-established neuropsychological test batteries were used, the Cambridge Automated Neuropsychological Test Battery –tower task which is based on Shallice's Tower of London (CANTAB-TOL) and the Delis-Kaplan Executive Function System

– tower task (D-KEFS-TOH) based on the Tower of Hanoi task. If these two tower tasks are functionally equivalent as measures of planning, then a similar pattern of deficits should be revealed for both tasks and the level of shared variance should be high.

The present study was also designed to investigate whether any planning deficits shown by the PD patients might be linked with specific cognitive processes. If the two tasks are not functionally equivalent then we could expect that different cognitive processes would be recruited in their solutions. Measures of working memory and inhibition were selected to investigate this as these have previously been found to be important for the successful execution of the tower tasks (Welsh, Satterlee-Cartmell, & Stein, 1999). Planned correlation and regression analyses were conducted to determine whether the relationships between task performance and cognitive skills were the same for both tower tasks and whether differences between PD patients and controls might be attributed to deficits in working memory or inhibition.

5.3.3 Methods

This study is part of a broader project examining cognitive, neuropsychiatric and language outcomes for patients with PD and received approval from the Canterbury Ethics Committee. Patients were on anti-parkinsonian medication and were tested while on optimal levels of medication (confirmed by patient report and also by observations made by the examiner).

Participants

Parkinson's disease group

PD patients in the Canterbury region who could be identified at the time of this study who did not have a diagnosis of dementia were invited by letter to participate. Patients were identified by two experienced neurologists and were required to meet the following inclusion criteria: 1) A diagnosis of idiopathic Parkinson's disease confirmed by a neurologist who specialised in motor disorders; 2) Assessed as Hoehn and Yahr stage I-IV (stage 1, n=8; stage 1.5, n=6; stage 2, n= 7; stage 2.5, n=10; stage 3, n=7; stage 4, n=2) (Hoehn & Yahr, 1967); 3) Aged between 50 and 80 years; 4) Adequate or corrected hearing and vision (self-report, checked by examiner); 5) Stable on PD medication; and 6) English as the primary spoken language.

Patients were excluded for the following reasons: 1. currently involved in a therapeutic trial or; 2. a history of: a) moderate or severe head injury,b) stroke or other neurological impairment, c) a major medical illness, d) significant psychiatric illness requiring hospitalisation, e) suspicion of dementia symptoms (Mini Mental Status Examine (MMSE) <25, (Folstein, Folstein, & McHugh, 1975), f) diagnosis of a learning disability, 3. major depressive episode in the previous 6 months, 4. pre-morbid IQ estimated at <85 using National Adult Reading Test (NART Nelson & Willison, 1991), 5. currently taking medications known to have a significant effect on the central nervous system (other than medications prescribed for the control of PD symptoms) or 6. presence of depression.

Of the 115 letters that were mailed, 6/115 (5.2%) of individuals with PD could not participate due to illness, 6/115 (5.2%) were deceased, 8/115 (6.9%) declined,

34/115 (29.6%) did not respond, and 21/115 (18.3%) did not meet the inclusion/exclusion criteria. After exclusions, 40 participants with PD were avaliable for inclusion in this study.

Controls

Controls were recruited from a number of sources including a previously established data base, advertisements at local clubs (bowling, hiking and table tennis) and businesses. All controls were given a brief outline of the study on first phone contact. If they were still willing to participate they were then sent an information sheet. In addition to adequate or corrected hearing and vision (self report, checked by the examiner) and being aged between 50 to 80 years of age, the same exclusion criteria listed above also applied to the control group.

Procedure

Assessments were carried out over two sessions which were scheduled at least one week apart. Tests were presented in a fixed order with breaks taken as required. Written consent was obtained from participants at the start of the first testing session after the study had been explained. Information pertinent to the inclusion/exclusion criteria was elicited from all participants during the first session using a semi-structured interview.

Demographic and Clinical information

Severity of motor symptoms was assessed using the Unified Parkinson's Disease Rating Scale (UPDRS) (Fahn & Elton, 1987) motor section and the Hoehn and Yahr (Hoehn & Yahr, 1967). Premorbid IQ was assessed using the National Adult Reading Test (NART) and mood was rated using the Beck Depression

Inventory-II (BDI-II) (Beck, Steer, & Brown, 1996). The Mini Mental Status Exam (MMSE) (Folstein, Folstein, & McHugh, 1975) and Dementia Rating Scale (Jurica, 2001) provided information regarding current mental status.

Cognitive Tests:

Cambridge Neuropsychological Test Automated Battery (CANTAB):

The CANTAB provides a computerized series of tasks using a touch sensitive screen. Three tasks from the CANTAB were used and included: 1. Stockings of Cambridge (CANTAB-TOL), 2. Spatial Span, and 3. Spatial Working Memory. Further details regarding the different tasks and procedures may be found in Owen, Downes, Sahakian, Polkey, & Robbins (1990).

Stockings of Cambridge (CANTAB-TOL) is a computerised version of the Tower of London (Shallice, 1982). For this task the participant was shown two displays of three colored balls. The participant was required to re-arrange the balls in the bottom half of the screen to match the arrangement in the top half of the screen. A total of 12 test problems were administered. The minimum number of moves required to solve each problem varied from two to five moves (2x2 move, 2x3 move, 4x4 move and 4x5 move). If a participant was unable to solve three consecutive problems in the maximum allowable number of moves the task was discontinued. Three outcome measures were generated from this task: Number of successfully completed problems, number of problems completed in the minimum number of moves, and total score. This last score was generated by adding the average number of moves for the two, three, four and five move problems. The maximum possible number of moves (two times the minimum number of moves plus one) was allocated to participants

who were unable to complete a given trial. Total possible scores ranged from a minimum of 14 to a maximum of 31 moves.

Spatial Span: The CANTAB spatial span task, a computerized version of the Corsi Block tapping task (Milner, 1971), was used to assess spatial working memory. In this task a random pattern of nine white boxes appeared on the screen. Some of the boxes changed color for a brief period to indicate a sequence. After a brief delay, the participant was required to touch the boxes in the same order that they had changed color. Sequences varied in length from two to nine boxes. If a participant failed to remember the sequence correctly another trial at that level was given. If the participant failed on the second trial at that level, the task was discontinued. Spatial span was determined by the longest sequence correctly remembered by the participant.

***Spatial Working Memory*:** For this task participants were required to find a blue token hidden in a group of randomly arranged boxes without looking in a box more than once. Boxes were opened by touching each one so that it opened revealing its contents. Once the token was found, the participant placed it in an empty column on the side of the screen. A new token was then hidden in a different box and the participant searched again. The process was repeated until all the boxes had been used to hide the token and the column at the side of the screen was filled. There were four practice trials, each with three boxes and then the test trials which included four trials with four, six, and eight boxes. Total number of boxes opened to complete all trials was used as a measure of spatial working memory performance with higher scores being indicative of poorer performance.

Daneman and Carpenter Reading Span Test (Daneman & Carpenter, 1980)-This test was used to assess the participants verbal working memory (Waters & Caplan, 1996b) and involved the presentation of sets of two to six sentences, each consisting of eight to 13 words. Each set of sentences had three trials with 60 sentences in total. Testing began with sequences of two sentences. Participants were asked to read each sentence out loud, judge the veracity of the statement, and remember the last word in each sentence (e.g., the hamburger bit into the juicy man). At the end of each trial, which was signaled by a blank card, the participant was asked to recall as many of the last words as possible. Spans ranged from 1.5-6. The test was discontinued if the participant was unable to remember the last word from any of the sentences in a trial set. The reading span was determined as the maximum number of sentences remembered with over 66% accuracy (two out of three trials correctly recalled). A ½ point was given if the participant remembered one of the sequences in a given trial.

Delis Kaplan Executive Functioning System (D-KEFS) (Delis, Kaplan, & Kramer, 2001): Two of the nine sub-tests were selected for use from this battery. Sub-tests were administered according to procedures outlined in the manual. For each sub-test, raw scores were converted to age corrected scaled scores (mean=10 and SD=3).

1. The D-KEFS-TOH consists of five discs which vary in diameter from large to small, and a board with three vertical pegs of equal size. For each of the nine problems the participant was presented with a picture of the tower to be built and two to five discs (depending on the level of difficulty of the tower) on the board in a predetermined starting position. Participants were asked to plan their moves prior to

starting while observing two rules: never place a larger disc on top of a smaller disc and only move one disc at a time. The task was discontinued after failure to complete three consecutive problems in the allotted time. Three scores were generated for this task, an age-adjusted total score, number of problems completed in minimum moves and total problems completed successfully. Because there is no maximum number of allowable moves, the total number of moves was not used as an outcome measure for this task. For the age-adjusted score, a raw score was first calculated that included bonus points which were allocated on the basis of the number of moves made and faster completion times.

2. Color-Word Interference Test: This test measured the participants' ability to inhibit automatic verbal responses. Participants were required to respond to four separate conditions. In the first condition, participants were presented with a page displaying rows of colored patches that they were required to name, and in the second condition they were given a page with rows of words that they were required to read. The third condition is the traditional "stroop effect" where the participants were presented with a page of words printed in dissonant ink colors and asked to name the color of the ink that the letters are printed in rather than reading the word. In the fourth and final condition, the inhibition switching task, participants were presented with a page with rows of words again printed in dissonant ink colors, but in this condition some of the words were in boxes. The participant was required to name the color of the ink for the words that were not in boxes but to read the word if the word was inside a box. For each condition, participants were required to name the colors or read the words as quickly as possible without skipping any or making any mistakes. Time taken to complete each condition was recorded and then converted to a

standardized score according to procedures outlined in the manual. The third and fourth conditions were used in this study as measures of inhibition.

5.3.5 Statistical Analysis

t- tests were used to compare PD patients versus healthy controls on clinical characteristics and for each of the tower tasks. Pearson's correlation was then used to examine the relationship between the two tower tasks and clinical and demographic status and also different measures of working memory and inhibition. Analysis of covariance (ANCOVA) was used for group comparisons to control for the effects of inhibition and, separately, working memory. Correlations between performance on the tower tasks and measures of working memory and inhibition were computed separately for PD patients and controls. Finally, multiple regression analysis was used to assess the influence of inhibition and working memory for performance on the CANTAB-TOL and separately for the D-KEFS-TOH.

5.3.6 Results

Patients were well matched to healthy controls in terms of age and pre-morbid IQ (Table 47), but differed in terms of symptoms consistent with low mood (as measured by the BDI-II) and current mental status (as measured by the MMSE and DRS-II), but no patient met the criteria for a depressive episode or dementia (DSM-IV criteria).

Table 47: Clinical and demographic characteristics, Parkinson's disease group versus controls.

	Parkinson's disease (n=40)		Control Group (n=40)			
	Mean	SD	Mean	SD	*t*-value	*p*-value
NART[1]	109.05	10.13	111.20	10.30	0.94	>0.30
Education(yrs)[2]	13.94	2.56	13.76	2.57	-0.30	>0.75
Age	66.15	6.65	66.58	5.47	0.31	>0.75
MMSE[3]	28.65	1.42	29.58	0.71	3.67	**<0.001***
BDI-II[4]	7.59	4.34	4.13	3.39	-3.96	**<0.001***
DRS-II[5]	10.53	2.12	11.45	2.11	1.82	<0.10
PD onset[6]	6.49	4.35				
UPDRS[7]	28.46	9.49				

[1]National Adult Reading Test used to estimate premorbid IQ, [2]Total number of years of formal education, [3]Mini Mental Status Exam,[4]Beck Depression Inventory-II;[5]Dementia Rating Scale-II; [6]Number of years since diagnosis of Parkinson's disease, [7]Unified Parkinson's disease Rating Scale (motor score component); *Significant group difference.

As shown in Table 48, the PD group performed more poorly than controls on the CANTAB-TOL, completing significantly fewer towers in the minimum number of moves and on average requiring more moves to solve the problems. The PD group also solved fewer CANTAB-TOL tower problems, but this difference fell short of significance ($p < 0.06$). By contrast, there were no differences between the groups on the D-KEFS-TOH (see Table 48). Effect sizes for outcome measures on the CANTB-TOL ranged from medium to large whereas those for the D-KEFS-TOH were all small. The PD group also showed deficits for two of the three working memory tasks (spatial span and reading span) and on both measures of inhibition.

Table 48: Parkinson's disease group compared to controls on two tower tasks and working memory tasks.

	Controls Mean (SD)	PD Patients Mean (SD)	*t*-value	*p*-value	Cohens *d*
CANTAB- TOL[1]					
Number solved in min move	8.1 (2.1)	6.6 (2.6)	2.81	**<0.01***	0.60
Number correctly solved	10.3 (1.6)	9.4 (2.8)	1.80	<0.06	0.39
Total number of moves used	18.1 (2.7)	20.1 (4.1)	2.62	**<0.02***	-0.58
D-KEFS TOH[3]					
Number solved in min move	4.2 (1.2)	4.1 (1.1)	0.50	>0.60	0.09
Number correctly solved	7.0 (1.7)	6.8 (1.5)	0.62	>0.50	0.13
Age adjusted scaled score	10.3 (3.1)	9.8 (2.6)	0.80	>0.40	0.17
Working Memory Tasks					
Spatial Span	5.2 (1.1)	4.6 (0.7)	2.78	**<0.01***	0.65
Spatial Working Memory[4]	186.6 (19.9)	195.0 (18.1)	1.97	<0.06	-0.44
Daneman & Carpenter	2.5 (0.7)	1.7 (0.6)	5.73	**<0.001***	1.23
Inhibition Tasks[5]					
Inhibition	11.6 (2.3)	9.1 (3.3)	3.87	**<0.001***	0.88
Inhibition Switching	11.8 (2.3)	9.1 (3.7)	4.0	**<0.001***	0.88

[1] Cambridge Automated Neuropsychological Test Battery- Stockings of Cambridge; [2] Total average number of moves made; [3] Delis-Kaplan Executive Function System Tower Task; [4] Total number of moves higher scores indicate greater impairment;[5] Delis-Kaplan Executive Function System Color-Word Interference Test. . *significant group difference.

Table 49: Correlations between Tower tasks and clinical and demographic measures for Parkinson's disease group.

	Nart [4]	Education Years	Age	MMSE [5]	BDI-II [6]	DRS-II [7]	PD Onset [8]	UPDRS [9]	H&Y [10]
CANTAB- TOL [1]									
Number in minimum moves	**0.32***	0.12	**-0.41****	**0.38***	0.03	**0.46****	-0.04	-0.15	-0.05
Number correctly solved	0.15	0.14	**-0.36***	**0.37***	0.04	**0.48****	-0.03	-0.20	-0.10
Total num of moves used [2]	-0.23	-0.07	**0.43****	**-0.37***	-0.06	**-0.45****	0.07	-0.18	0.10
D-KEFS TOH [3]									
Number in minimum moves	0.27	0.24	-0.28	0.04	-0.17	**0.41****	0.09	-0.03	-0.07
Number correctly solved	0.23	0.07	-0.29	0.27	-0.07	0.24	-0.05	-0.29	-0.28
Age-adjusted scaled score	**0.35***	0.28	-0.29	0.08	-0.14	**0.34***	-0.22	-0.16	-0.20

[1] Cambridge Automated Neuropsychological Test Battery- Stockings of Cambridge; [2] Total average number of moves made; [3] Delis-Kaplan Executive Function System Tower Task; [4] National Adult Reading Test used to estimate premorbid IQ; [5]Mini Mental Status Exam; [6]Beck Depression Inventory-II, [7] Dementia Rating Scale-II, [8]Number of years since diagnosis of Parkinson's disease,[9]Unified Parkinson's disease Rating Scale (motor score component); [10]Hoehn & Yahr stage, * significant at $p<0.05$; ** significant at $p<.001$

To enable a direct comparison between the CANTAB-TOL and D-KEFS-TOH, the total number of towers completed in minimum moves and total number of towers correctly solved were converted to percentage scores. On average the PD patients solved only 55.2% of the CANTAB-TOL problems in the minimum number of moves while the matched controls solved 65.5%. However, both groups solved a similar number of problems in the minimum number of moves for the D-KEFS-TOH, with the PD and healthy controls group solving 45.3% and 46.6% of problems respectively. In terms of the average total number of towers correctly solved, PD patients solved 78.3% of CANTAB-TOL problems compared to 86.0% for controls, and 75.5% of D-KEFS-TOH problems compared to 78.1% for controls.

Table 49 shows the relationship for PD patients between performance on the tower tasks and measures of clinical and demographic status. For performance on the CANTAB-TOL, significant correlations were evident with age and current mental status (as measured by the MMSE and DRS-II). There was also a significant positive correlation for the CANTAB-TOL problems completed in the minimum number of moves and pre-morbid IQ (see Table 49). The only significant correlations between performance on the D-KEFS-TOH were found between the age-adjusted tower score pre-morbid IQ, and DRS-II, and between towers conducted in the minimum number of moves and DRS-II score.

As can be seen in Table 50, only low-to-moderate correlations were found for PD patients on the two tower tasks (r=.27 to r=-.49), indicating that between 7-24% of variance in the tasks was shared. In terms working memory measures, only spatial span showed a significant positive correlation with all outcome measures on CANTAB–TOL. Spatial working memory was only significantly associated with the

number of towers solved in minimum moves, and the verbal working memory task was significantly associated only with the number of towers correctly solved (see Table 50). Both measures of inhibition showed a moderate correlation with the CANTAB-TOL. A stronger pattern was evident between performance on the D-KEFS-TOH and measures of working memory with significant positive correlations evident for both spatial span and spatial working memory. There were no significant correlations between verbal working memory and only one measure of inhibition was associated with the D-KEFS-TOH (see Table 50).

The level of shared variance between the two tower tasks for healthy controls was similar to that for PD patients (r=.28 to r=-.61; 7-37% shared variance), but the pattern of performance across related tasks differed (see Table 51). Among measures of working memory, only spatial working memory was significantly correlated with tower performance. This finding was consistent across both tasks. By contrast, there were no significant correlations with the spatial span task or verbal working memory for both the CANTAB-TOL and D-KEFS-TOH (see Table 51). Inhibition was related to performance on the CANTAB-TOL but not with performance on any aspect of the D-KEFS-TOH.

Table 50: Correlations between Tower of Hanoi, Tower of London, Working Memory and Inhibition measures for Parkinson's disease patients.

	CANTAB-TOL (N) Solved in min moves	CANTAB-TOL (N) correctly solved	CANTAB-TOL Total number of moves	D-KEFS-TOH (N) solved in min moves	D-KEFS-TOH (N) correctly solved	D-KEFS-TOH Age adjusted scaled score	Spatial Span	Spatial Working Memory	Inhibition
CANTAB- TOL[1]									
(N) Solved in min moves									
(N) correctly solved	**0.88*** **								
Total number of moves [2]	**-0.94*** **	**-0.92*** **							
D-KEFS-TOH[3]									
(N) solved in min moves	**0.39***	0.27	**-0.41****						
(N) correctly solved	**0.46****	**0.43****	**-0.49****	**0.41***					
Age adjusted scaled score	**0.44****	**0.35***	**-0.47****	**0.80*** **	**0.79*** **				
Working Memory Tasks									
Spatial Span	**0.37***	**0.47****	**-0.41****	0.26	**0.46****	**0.36***			
Spatial Working Memory[4]	**0.34***	0.15	-0.28	**0.42****	**0.41****	**0.53****	-0.23		
Reading Span[5]	0.30	**0.38***	-0.30	0.09	0.30	0.20	**0.43****	**-0.36***	
D-KEFS Color Word[6]									
Inhibition	**0.49****	**0.48****	**-0.53****	**0.38***	**-0.41****	**0.40***	**0.45****	**-0.34***	
Inhibition Switching	**0.43****	**0.36***	**-0.45****	0.21	0.14	0.25	**0.36***	-0.20	**0.50****

[1] Cambridge Automated Neuropsychological Test Battery- Stockings of Cambridge; [2] Total average number of moves taken [3]Delis-Kaplan Executive Function System Tower Task; [4] Scores for this task were inverted so that a higher score indicated good performance. [5] Daneman and Carpenter Reading Span Task; [6] Deli-Kaplan Executive Function System Color Word Interference Task; *p<0.05; **p<0.01; ***p<0.001

Table 51: Correlation between Tower of Hanoi, Tower of London, working memory and inhibition measures for healthy controls.

	CANTAB-TOL (N) Solved in min moves	CANTAB-TOL (N) correctly solved	CANTAB-TOL Total number of moves	D-KEFS-TOH (N) solved in min moves	D-KEFS-TOH (N) correctly solved	D-KEFS-TOH Age adjusted scaled score	Spatial Span	Spatial Working Memory	Inhibition
CANTAB- TOL[1]									
(N) Solved in min moves									
(N) correctly solved	**0.79*** **								
Total number of moves [2]	**-0.89*** **	**-0.87*** **							
D-KEFS-TOH[3]									
(N) solved in min moves	**0.56*** **	**0.57*** **	**-0.61*** **						
(N) correctly solved	0.28	**0.46** **	**-0.34***	**0.54** **					
Age adjusted scaled score	**0.36***	**0.52** **	**-0.43** **	**0.83*** **	**0.83*** **				
Working Memory Tasks									
Spatial Span	0.18	0.28	-0.28	0.25	0.12	0.21			
Spatial Working Memory[4]	**0.47** **	**0.59*** **	**-0.57*** **	**0.62*** **	**0.41***	**0.47** **	-0.23		
Reading Span[5]	0.004	0.06	0.02	-0.09	0.05	0.01	0.18	-0.09	
D-KEFS Color Word[6]									
Inhibition	**0.38***	0.26	-0.27	0.09	0.02	0.06	**0.38***	-0.17	
Inhibition Switching	**0.43** **	0.21	**-0.38***	0.10	-0.01	-0.10	0.11	-0.23	**0.41***

[1] Cambridge Automated Neuropsychological Test Battery- Stockings of Cambridge; [2] Total average number of moves taken [3]Delis-Kaplan Executive Function System Tower Task; [4] Scores for this task were inverted so that a higher score indicated good performance; [5] Daneman and Carpenter Reading Span Task; [6] Deli-Kaplan Executive Function System Color Word Interference Task; *p<0.05; **p<0.01; ***p<0.001

Separate ANCOVAs were used to assess whether group differences observed for the CANTAB-TOL remained significant after controlling for working memory and inhibition. Spatial working memory from the CANTAB was selected as a covariate because it was the only working memory measure to have a significant association with performance on the tower tasks for both controls and PD patients (see Tables 50 and 51). Similarly, simple inhibition was chosen as a covariate for inhibition, because it was the measure of inhibition that most strongly correlated with tower performance for both the controls and PD patients (see Tables 50 and 51). With spatial working memory as a covariate, group differences were still evident for the number of tower problems on the CANTAB-TOL solved in the minimum number of moves (F=4.64, df=77, p<0.05). However, there were no longer significant group differences for the number of towers solved correctly or the total number of moves used (F= 1.50, df=77, p>0.25 and F=3.77, df=77, p<0.06 respectively). With simple inhibition as a covariate there were no significant group differences for number of problems solved in the minimum number of moves (F=1.27, df=77, p > .30), total number of towers solved (F=0.04, df=77, p > .90) or total number of moves used (F=0.86, df=77, p > .40).

Finally, regression analyses were conducted to test whether deficits shown by the PD patients on the CANTAB-TOL task were due to deficits in spatial working memory, inhibition, or both. For these analyses, group (PD vs control) and spatial working memory (or simple inhibition) was entered at the first step, and simple inhibition (or spatial working memory) was entered at the second step. When group and spatial working memory were entered in the first step, inhibition was significantly related to the number of towers solved in minimum moves ($\beta = 0.39$, R^2 change =

0.12, $p < 0.001$), the number of towers correctly solved ($\beta = 0.39$, R^2 change = 0.12, $p < 0.001$) and the total number of moves ($\beta = -0.31$, R^2 change = 0.12, $p < 0.001$). Conversely, spatial working memory was significantly related to all outcome measures when group and inhibition were entered on the first step (minimum number of moves, $\beta = 0.30$, R^2 change = 0.08, $p < 0.01$, total number of towers solved, $\beta = 0.22$, R^2 change = 0.04, $p < 0.05$ and total number of moves $\beta = -0.39$, R^2 change = 0.08, $p < 0.01$). This suggests that impairments in both spatial working memory and inhibition are necessary to account for the deficits in CANTAB-TOL performance observed in the PD patients relative to controls.

For the D-KEFS-TOH simple inhibition was not significantly related to any of the outcome measures when entered at the second step (number of towers solved in minimum moves, $\beta = 0.14$, R^2 change < 0.01, $p < 0.25$; total number of towers solved, $\beta = 0.21$, R^2 change < 0.03, $p < 0.10$ and for the scaled score, $\beta = 0.15$ R^2 change < 0.02, $p < 0.25$). However, when group and inhibition were entered in the first step, spatial working memory was significantly related to D-KEFS-TOH performance in terms of the number of towers solved in minimum moves ($\beta = 0.51$, R^2 change = 0.23, $p < 0.001$), the number of towers correctly solved ($\beta = 0.37$, R^2 change = 0.12, $p < 0.01$) and the scaled score ($\beta = 0.47$, R^2 change = 0.20, $p < 0.001$). This suggests that spatial working memory is a stronger determiner of performance on the D-KEFS-TOH than simple inhibition.

5.3.7 Discussion

The main objective of this study was to compare two planning subtests of two well-established neuropsychological test batteries with respect to their sensitivity to detect planning impairments in patients with PD. To this end, we used the tower tasks from the Cambridge Automated Neuropsychological Test Battery (CANTAB-TOL) and the Delis-Kaplan Executive Function System (D-KEFS-TOH). In addition, measures of working memory and inhibition were also utilized. Compared to matched controls, medicated PD patients without dementia were impaired on the CANTAB-TOL but not the D-KEFS-TOH. PD patients also performed more poorly on measures of working memory and inhibition when compared to matched controls. Moderate correlations were obtained for PD patients between performance on the two tower tasks, and with measures of working memory and inhibition. By contrast, for healthy controls there was little association between performance on the tower tasks and measures of inhibition, and only one of the three working memory tasks was significantly related to performance on either of the tower tasks. Spatial working memory and inhibition was related to performance on the TOL task but the contribution of inhibition to the TOH was much weaker. This finding was confirmed using regression analysis which showed that whereas performance on the CANTAB-TOL task was dependent on inhibition and spatial working memory, performance on the D-KEFS-TOH was dependent on spatial working memory only. These findings suggest that the CANTAB-TOL and the D-KEFS-TOH require different cognitive skills and should not be considered interchangeable measures of planning ability for use with PD patients.

These findings are consistent with previous research, using healthy younger participants, which reported that a significant amount of non-shared variance exists between the two tower tasks (Welsh, Satterlee-Cartmell, & Stein, 1999). Further, previous research has also found evidence for the recruitment of different cognitive processes when solving the TOH compared to the TOL (Welsh, Satterlee-Cartmell, & Stein, 1999; Zook, Davalos, DeLosh, & Davis, 2004). For example, Handley et al., (2002) reported that the TOH task correlated more highly with spatial memory capacity but not complex verbal working memory. Consistent with this finding, in the present study, D-KEFS-TOH performance was only correlated with (visuo-) spatial but not verbal aspects of working memory. Welsh, Satterlee-Cartmell and Stein (1999) found that working memory and inhibition was strongly related to performance on the TOL task but the contribution of inhibition to the TOH was much weaker.

Apart from the obvious physical structures of the two tower tasks, there are a number of possible reasons why these two tasks might vary in relation to the recruitment of cognitive processes. Firstly, the D-KEFS-TOH requires participants to plan for problems that require between 1-26 moves for perfect execution. On the other hand, the CANTAB-TOL task problem set only requires 2-5 moves. Although both tasks instruct the participant to plan their moves prior to engaging in the task, it is likely that for many of the moves for the D-KEFS-TOH participants engage in "on line planning", that is they plan moves while they are engaged in the task rather than planning all the moves before beginning the task. This is most likely because more complex problems in the TOH task are substantially based on recursive shuffling of discs (in contrast to the TOL) which would be difficult to plan out in full prior to beginning the task (Newell & Simon, 1972). Secondly, there may be floor effects

associated with D-KEFS-TOH. Although problems are graded, with easier problems being presented first and more difficult ones later, problems move rapidly from those that nearly all participants can solve in minimum moves to problems that only a few can solve, thus reducing the sensitivity of the task. Further, only one problem is presented at each level of difficulty and there are no introductory problems. By contrast the CANTAB-TOL presents a number of introductory problems and more than one problem at each level.

On the other hand, the CANTAB-TOL uses the original set of problems as outlined by Shallice (1982), which are nested in that earlier problems may form part of later problems. As a result, performance may depend to some extent on participants' learning across the problem set and thus the CANTAB-TOL may not represent a test of pure planning ability. It has previously been reported that PD patients have problems with learning, even in the early stages of the disease (Buytenhuijs et al., 1994), thus controls may benefit more from the nesting of CANTAB-TOL problems than PD patients.

As Berg and Byrd (2002) point out, the lack of consistency in findings between different tower tasks could be related to a number of issues including: 1) The actual differences in the tower structure; 2) Insufficient attention to the difficulty of the problem set; and 3) Variation in performance measures. Given these caveats it is difficult to make direct comparisons between the D-KEFS-TOH and the CANTAB-TOL. Further, it seems likely that both present potential confounds in terms of the problems sets that are used. Nevertheless the CANTAB-TOL was the more sensitive task as despite these potential problems it was still able to detect significant differences between the PD group and controls, in contrast to the D-KEFS-TOH.

Planning in Parkinson's Disease: A Matter of Problem Structure?

(In press journal Neuropsychologia avaliable on line August 2007)

5.4.1 Abstract

Although the Tower of London (TOL) has been extensively used to assess planning ability in patients with Parkinson's disease (PD), the reported presence or extent of any planning deficits has been inconsistent. This may partly be due to the heterogeneity of the TOL tasks used and a failure to consider how structural problem parameters may affect task complexity. In the present study, planning in PD patients was assessed by systematically manipulating TOL problem structure. Results clearly disprove the identity assumption of problems with an equal number of minimum moves. Instead, substantial parts of planning performance were related to more subtle aspects of problem structure, such as subgoaling patterns and goal hierarchy. Planning in PD patients was not impaired in general but was affected when the information provided by the problem states was ambiguous in terms of the sequential order of subgoals, but not by increases in search depth.

5.4.2 Introduction

In addition to its well-known motor symptoms, Parkinson's disease (PD) is associated with a number of cognitive deficits, including planning. To plan successfully, an individual must look ahead through a series of possible steps, some of which may be counterintuitive, to reach a desired goal. The ability to plan is an essential part of daily living, and difficulties with this skill may negatively affect autonomy and quality of life. Planning deficits in PD have been found even in the early stages of the disease process (Culbertson, Moberg, Duda, Stern, & Weintraub, 2004; Hodgson, Tiesman, Owen, & Kennard, 2002; Morris et al., 1988; Owen et al., 1992), and may reflect the fronto-striatal circuit degeneration associated with this disorder (Owen, 2004a). One of the most common tasks used to measure planning ability in PD is the Tower of London (TOL; Shallice, 1982). However, the literature is inconsistent with regard to the presence or exact nature of any planning deficits in PD, possibly reflecting the variation of TOL tasks applied[6]. Further, non-uniform procedures and problem sets have been used, making it difficult to compare results across studies. To effectively assess planning deficits in PD a more systematic consideration of these issues is required (Taylor & Saint-Cyr, 1995).

Recent research has emphasized the selection of specific tower problems because it has been suggested that different aspects of individual problems may increase or decrease the level of task complexity, and therefore the cognitive demands for planning (Berg & Byrd, 2002). At the most basic level, the minimum number of moves can be viewed as an indication of how difficult a particular problem is. However, difficulty may be influenced by more than just the number of moves

[6]For instance, Culbertson et al., (2004) reported a group of PD patients performing significantly worse than controls in terms of average number of moves, while Morris et al.,(1988) previously found no differences in accuracy but only for planning times.

required for solution. For example, problems with the same number of moves may have a different search depth or subgoaling pattern. A subgoal move refers to moves that are essential to the solution of a given problem, but do not place the ball into its goal position (Ward & Allport, 1997). Search depth is defined as the number of subgoal moves before the first ball can be placed into a goal space(Spitz, Webster, & Borys, 1982). In TOL problems, search depth is related to mainly two predominant subgoaling patterns (Kaller, Unterrainer, Rahm, & Halsband, 2004). Specifically, optimal solutions of five-move problems either require (1) sequences of two initial subgoal moves followed by three goal moves; or (2) sequences of a subgoal move followed by a goal move, another subgoal move, and two final goal moves (Figure 19-A). As a result, five-move TOL problems feature search depths of either two or one initial subgoal moves, respectively.

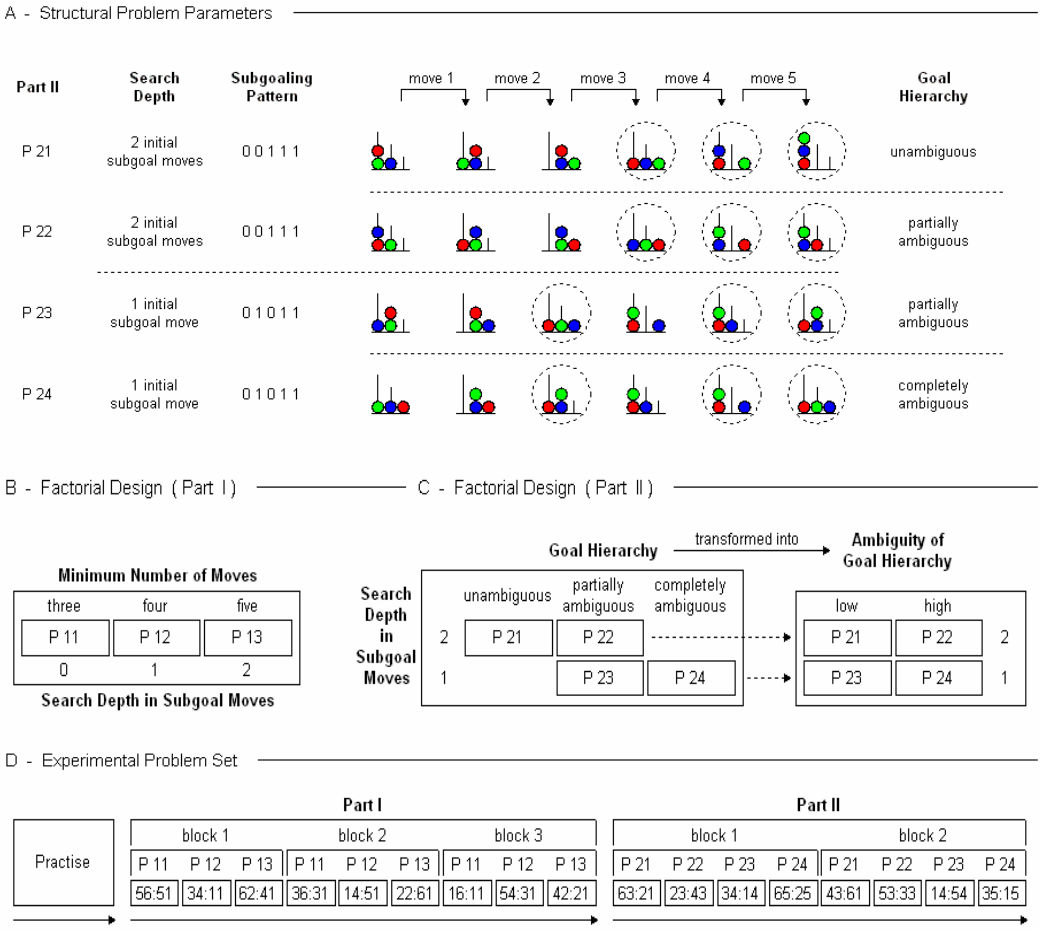


Figure 19: (A) Structural Problem Parameters, (B) Factorial Design (Part I), (C) Factorial Design (Part II), (D) Experimental Problem Set.

(A) *Structural Problem Parameters*. Illustrations of goal hierarchy and search depth are exemplified on five-move TOL problems that were applied in Part II of the experiment. Four different types of problems were administered (P21-P24). In the TOL, two predominant subgoaling patterns are evident causing "search depths" of either one (P23, P24) or two initial subgoal moves (P21, P22). Goal hierarchy relates to the three possible configurations of the goal state: "tower" (P21), "partial tower" (P22, P23), and "flat" structures (P24) differentially predispose the consecutive order of the final goal moves and the associated subgoal sequences. Goal moves and subgoal moves are indicated by digits '1' and '0', respectively. Dashed circles around problem states denote goal moves. (B) *Factorial Design (Part I)*. For the assessment of general planning ability, search depth was step-wise increased in combination with the minimum number of moves (P11-P13). Goal hierarchy was kept unambiguous by using only goal states with "tower" structures. Problems featured only one optimal path to solution and no suboptimal alternatives. (C) *Factorial Design (Part II)*. In the second part, the influence of goal hierarchy and search depth on planning performance was systematically manipulated in a set of five-move problems (P21-P24) while controlling for other influences of problem structure. (D) *Experimental Problem Set*. Numbers in boxes at the bottom denote start state and goal state of presented problems in the notation suggested by Berg & Byrd (2002).

Goal hierarchy is another aspect of problem structure that affects task complexity (Ward & Allport, 1997). Goal hierarchy is related to the ambiguity of information on subgoal ordering, that is, the degree to which the sequence of the final goal moves can be derived from the configuration of the goal state (Kaller, Unterrainer, Rahm, & Halsband, 2004). For example, problems with "tower" goal states, where all three balls are stacked on a single rod, provide an unambiguous goal hierarchy because the ball at the bottom has to be placed in its goal position before the ball that is second from the bottom, and so on. By contrast, no such information can be derived from "flat" goal states (Figure 19-A). Problems may also vary concerning the number of optimal paths to solution which refer to the number of different possible solutions that allow the problems to be solved in the minimum number of moves (Newman & Pittman, in press; Unterrainer, Rahm, Halsband, & Kaller, 2005). In addition, there may also be suboptimal alternatives that take more than the minimum number of moves, but allow the first ball to be placed into its goal position within a number of moves equal to the optimal solution (Kaller, Unterrainer, Rahm, & Halsband, 2004).

Given the variety of the aforementioned aspects of problem structure, it seems plausible to assume that systematic manipulations of TOL problem parameters will have differential effects on planning performance, in particular with respect to clinical populations that are known to have planning impairments. The aims of the present study are hence twofold. First, to test the widespread assumption of identical task complexity for problems with an equal number of minimum moves. The apparent popularity of this assumption seems to be implicated to some extent by the large number of studies using minimum moves as the only indicator of problem difficulty, without any consideration of other structural problem parameters. The second goal

was to test the hypothesis that planning ability of PD patients is more severely affected in problems that, irrespective of the minimum number of moves, have higher demands on active manipulation of spatial information within working memory and identification and implementation of organizational strategies (Cools, 2006; Owen, 2004b). Thus, in the present study the effects of systematic manipulations of problem structure were examined in terms of goal hierarchy and search depth.

5.4.3 Methods

Participants

The study was approved by the local ethics committee and all participants gave written informed consent prior to participation. Participants were recruited from a data base of PD patients and healthy controls. Thirty non-demented and non-depressed patients with idiopathic PD diagnosed by a neurologist who specialized in movement disorders were assessed (see Table 52 for inclusion/exclusion criteria). All patients were on anti-Parkinsonian medication and were tested while on optimal levels. Thirty healthy controls were individually matched in terms of age and pre-morbid intelligence.

Assessments were carried out at the University of Canterbury over two testing sessions. Tests were presented in a fixed order with breaks taken as required. Planning ability was assessed using the TOL at the beginning of the second session[7].

[7] Full information regarding tower structures used and the order of presentation can be found in appendix (XXVIII)

Table 52: Inclusion and exclusion criteria.

The same criteria were also applied for the selection of healthy controls with the exception of issues related to diagnosis and medical treatment of Parkinson's disease.

Inclusion criteria:

- Diagnosis of idiopathic Parkinson's disease, assessed as between Hoehn and Yahr (1967) stage I-III
- Aged between 50 and 80 years, English as the primary spoken language, adequate or corrected hearing and vision (self-report checked by examiner)

Exclusion criteria:

- History of moderate or severe head injury, stroke or other neurological impairment, major medical illness, psychiatric illness requiring hospitalisation
- Currently involved in a therapeutic trial
- Suspicion of dementia (MMSE<25), diagnosis of learning disability, pre-morbid IQ<85 (NART)
- Acute depression or major depressive episode in the previous six months (BDI-II>17; DSM IV)
- Taking other than anti-Parkinsonian medication known to have significant effects on the central nervous system

Demographic and Clinical Information

Pre-morbid intelligence was estimated using the National Adult Reading Test (NART; Nelson & Willison, 1991). Current cognitive status was examined by the Mini Mental Status Exam (MMSE, Folstein, Folstein, & McHugh, 1975) and the Dementia Rating Scale (DRS-2; Jurica, Leitten, & Mattis, 2001). The Beck Depression Inventory-II (BDI-II; Beck, Steer, & Brown, 1996) was applied as a measure of affective disturbances. In addition to the Hoehn and Yahr (1967), severity of motor impairment was assessed the Unified Parkinson's Disease Rating Scale (UPDRS; Fahn & Elton, 1987). Demographic and clinical characteristics for PD patients vs healthy controls is shown in Table 53.

Table 53: Sample descriptions in terms of demographic and clinical information.

	Controls Mean (SD)	**PD** Mean (SD)	**t-value**	**p-value**
Age	66.43 (5.3)	65.77 (6.6)	0.43	> .65
EDU[1]	13.78 (2.7)	14.08 (2.8)	0.42	> .65
NART[2]	111.67 (10.8)	109.93 (10.8)	0.70	> .45
MMSE[3]	29.70 (0.5)	28.90 (1.2)	3.44	< .01
DRS-2[4]	12.07 (2.6)	10.60 (1.8)	2.52	< .05
BDI-II[5]	3.33 (2.6)	8.60 (3.8)	5.29	< .001
PD-Ons[6]	-	58.5 (8.8)	-	-
PD-Dur[7]	-	7.3 (4.6)	-	-
H&Y[8]	-	2.30 (0.6)	-	-
UPDRS[9]	-	27.13 (7.5)	-	-

[1] Total years of education;[2] National Adult Reading Test;[3] Mini Mental Status Exam; [4] Dementia Rating Scale;[5] Beck Depression Rating Scale; [6] Age of onset (in years); [7] duration of disease (in years);[8] Hohen & Yarh; [9] Unified Parkinson's disease Rating Scale.

Although there were significant differences between the two groups in terms of mood ratings (BDI-II) and cognitive status (MMSE, DRS-2), none of the PD patients showed any evidence of clinical depression or dementia (see Table 53).

Planning Task and Instructions

A computerized version of the TOL was used to assess planning ability. Start and goal states were presented in the lower and upper half of the screen, respectively. Participants were instructed to transform the start state into the goal state while following three rules: (1) only one ball may be moved at a time; (2) a ball cannot be moved while another is lying on top of it; and (3) three balls may be placed on the tallest rod, two balls on the middle rod, and one ball on the shortest rod. Participants

were instructed to solve each problem in the minimum number of moves (indicated on the screen). To match the goal state, participants had to operate on the start state. Movements were executed on an ELO 17" touch sensitive screen. Individual trials were initiated by the experimenter. Before displaying the next problem, participants were prompted by the program to plan ahead first. Prior to the experimental trials, participants were familiarized with the TOL and the handling of the touch screen in a practice phase using two- and three-move problems.

Experimental Design

The assessment of planning ability occurred in two parts. The objective of Part I was to examine whether planning in PD was generally impaired even in highly structured and well-defined situations. Therefore, the minimum number of moves was systematically increased from three to five moves while problems featured only a totally unambiguous goal hierarchy. This enabled search depth, but no other confound, to be varied systematically (together with minimum number of moves) from zero to two initial subgoal moves before the first goal move (Figure 19-B). In addition, problems had only one optimal path for solution but no suboptimal alternatives.

A more complex scenario was examined in Part II by systematically varying search depth and goal hierarchy in a set of five-move problems (Figure 19-A and 19-C). In contrast to Part I, the applied problems also featured alternative paths leading to suboptimal solutions. The minimum number of five moves for these TOL problems could only be achieved by one optimal path for solution. The specific aim of Part II was to disentangle the contributions of two specific aspects of problem

structure, that is, search depth and goal hierarchy, to planning impairments in PD patients, while the minimum number of moves was kept constant.

The factorial designs of both Part I and II are illustrated in Figure 19-B and 19-C, respectively. Due to general features of the TOL problem space, the combination of both search depth and goal hierarchy in Part II inevitably results in an imbalanced design since certain problem configurations simply do not exist. Testing for possible interactions between goal hierarchy and search depth would therefore be unfeasible (Winer, 1962). However, to allow for a factorial analysis of the interesting main effects and interactions with group, the composition of the two structural problem parameters was transformed into a hierarchical design by nesting the relative ambiguity of subgoal ordering (i.e., goal hierarchy) under the levels of search depth (Figure 19-C). The resulting problem set is shown in Figure 19-D. Within Parts I and II, problems were presented block-wise using a fixed order within blocks. Across blocks, different isoforms of problems were applied using pseudo-randomized permutation of ball colours. More detailed information on the selection of structurally unique problems and the balancing of isoforms (Berg & Byrd, 2002) can be obtained from the corresponding authors.

Measures

For the analyses reported below, accuracy of problem solutions was recorded. The terms 'performance' and 'accuracy' are henceforth used interchangeably and refer to the percentage of problems correctly solved in the minimum number of moves.

5.4.4 Results

Part I

Performance in the first part of the experiment was almost at ceiling for both healthy controls and PD patients (Table 54). A two-way repeated-measures ANOVA on accuracy revealed a significant main effect for the minimum number of moves [$F(2,58)=6.81$, $p=.002$, $\eta^2=.105$], but no main effect for group [$F(1,58)=.11$, $p=.742$, $\eta^2=.002$] or interaction between factors [$F(2,58)=.55$, $p=.577$, $\eta^2=.009$]. Post-hoc pair-wise comparisons yielded significant differences between three-move problems and four- as well as five-move problems ($p<.005$) but performance in four- and five-move problems proved to be equally difficult ($p=.993$).

Table 54: Part I – Mean percent of Tower Of London problems correctly solved, listed separately for the Parkinson's disease patients and healthy controls.

Part I	**three moves**	**four moves**	**five moves**
Controls	100.0 % (0)	92.3 % (3.1)	94.4 % (3.2)
PD	98.9 % (1.1)	93.4 % (3.7)	91.2 % (3.9)

Numbers in parentheses denote the standard error of mean.

Part II

As is evident from Figure 20, performance in five-move problems could be systematically attributed to the experimental manipulations of problem structure. A three-way repeated-measures ANOVA on accuracy yielded significant main effects for search depth [$F(1,58)=22.31$, $p<.001$, $\eta^2=.278$] and goal hierarchy [$F(1,58)=9.12$, $p=.004$, $\eta^2=.137$] but not for group [$F(1,58)=.53$, $p=.472$, $\eta^2=.009$]. In addition, the interaction between group and goal hierarchy was significant [$F(2,58)=4.70$, $p=.034$, $\eta^2=.075$]. Post-hoc analyses confirmed a highly significant effect of goal hierarchy in the PD group ($p<.001$) but not for controls ($p=.580$). That is, planning performance of PD patients was, in contrast to healthy controls, specifically affected by increased ambiguity of goal hierarchy. None of the remaining interactions was found to reach statistical significance [all $F(1,58)<.5$, $p>.5$, $\eta^2<.01$].

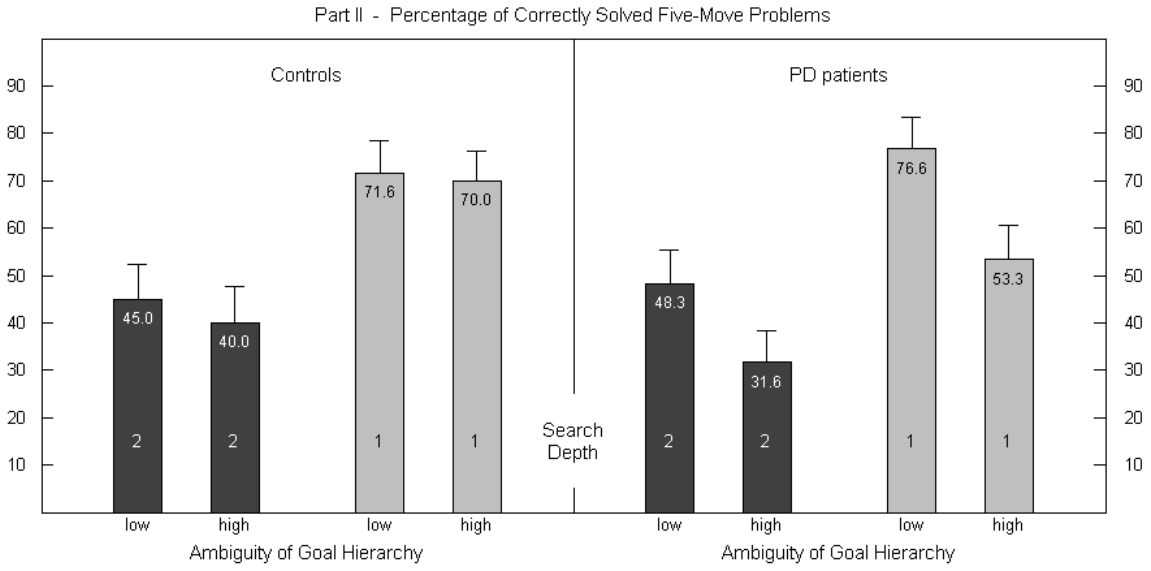


Figure 20: Part II – mean performance in percent, plotted separately for the Parkinson's disease group versus healthy controls and according to the experimental manipulation of problem structure, that is, search depth and ambiguity of goal hierarchy.

Note that in part II, all problems had an equal minimum number of five moves for optimal solution. Error bars denote the standard error of mean.

To preclude that a possibly existing interaction between search depth and group had been simply masked due to the interleaved shifting of goal hierarchy within the nested design, an additional two-way repeated-measures ANOVA was conducted on search depth (cells P22 and P23, Figure 19-C) and group. That is, the effects of search depth and group were directly tested in those problems that featured a partially ambiguous goal hierarchy. In line with the analysis reported above, results again revealed a significant main effect solely for search depth [$F(1,58)=27.77$, $p<.001$, $\eta^2=.324$], but neither a main effect of group [$F(1,58)=.07$, $p=.800$, $\eta^2=.001$] nor an interaction [$F(1,58)=.84$, $p=.363$, $\eta^2=.014$].

5.4.5 Discussion

The results of this study revealed that planning in PD patients was generally intact when the ambiguity of the planning situation was reduced to a minimum (Part I). In such cases, PD patients correctly solved even five-move problems with an accuracy of greater than 90 percent. However, it was also found that planning performance of PD patients substantially declined if the ambiguity of goal hierarchy was increased (Part II). That is, compared to normal controls, PD patients exhibited a discernable planning deficit only in those problems with less predictable subgoal sequences.

With respect to the first aim of this study, these results strongly challenge the wide-spread assumption that problems with an equal minimum number of moves also feature an identical level of task difficulty. Instead, the present results suggest that problems with an equal minimum number of moves do not necessarily have to share identical task difficulty (*within-level variability*), nor does a gradual increase of minimum moves necessarily imply a correlated rise of task difficulty (*between-level invariability*). This conclusion is supported by previous research on the psychometric properties of the TOL (Culbertson, Moberg, Duda, Stern, & Weintraub, 2004; Humes, Welsh, Retzlaff, & Cookson, 1997; Kafer & Hunter, 1997; Schnirman, Welsh, & Retzlaff, 1998) as well as by studies explicitly addressing the impact of problem structure on planning (Carder, Handley, & Perfect, 2004; Kaller, Unterrainer, Rahm, & Halsband, 2004; Newman & Pittman, in press; Unterrainer, Rahm, Halsband, & Kaller, 2005; Ward & Allport, 1997).

With respect to the second aim of this study, planning performance of PD patients was indeed specifically associated with systematic manipulations of structural

problem parameters (Part II). PD patients were not impaired in general but only affected when the information provided by the goal state was ambiguous with respect to the sequential order of subgoals. PD patients were, however, no more liable to increases in search depth than healthy controls (Figure 20). These results are particularly pertinent in the light of a recently proposed framework on the distinct roles that are played by the striatum and the prefrontal cortex in the flexibility and stability of cognitive representation, respectively (Cools, 2006). Given a prevalence of dopamine depletion particularly in the dorsal striatum, PD patients with mild to moderate symptoms are supposed to exhibit a dissociable pattern of impaired active reorganization and manipulation of working memory contents, while maintenance of information is preserved (Owen, 2004). These opposing predictions seem to be also reflected in the present results because a PD-specific deficit was observed for TOL problems with higher ambiguous goal hierarchy but not for increases in search depth. Goal hierarchy affects the "degrees of freedom" of the planning situation by more or less explicitly determining the sequential order of single steps on the solution path (Kaller, Unterrainer, Rahm, & Halsband, 2004; Ward & Allport, 1997). Higher ambiguity of goal hierarchy should therefore be associated with increasing demands on cognitive flexibility, that is, the active implementation of organizational strategies in order to search and generate the optimal sequence of moves (Cools, 2006; Owen, 2004). Thus, in the absence of direct guidelines that are explicitly provided by the configuration of the goal states, PD patients would consequently be expected to exhibit less efficient planning abilities (see also Taylor & Saint-Cyr, 1995), as was observed in the present study. In contrast, given a likely "anchoring" function of the first goal move and the chunking of subgoal-move sequences (Ward & Allport, 1997), increases of search depth might primarily relate to aspects of working memory

maintenance. Because working memory is generally not affected in mild to moderate stages of the disease (Owen et al., 1992) PD patients would accordingly not be expected to show any specific planning deficits in problems with larger search depths, which is again consistent with the present results. However, increases in search depth are, at least to some extent, also associated with higher demands on strategic look-ahead (Spitz, Webster, & Borys, 1982) that, unlike the present study, might cause a PD-related decline in accuracy. Likewise, accomplishing suboptimal alternatives might also increase demands on cognitive flexibility as misleading paths, if recognized, have to be circumvented by searching an optimal solution. Present data[8], however, do not suggest such an association. Instead, participants did not necessarily become aware of when they had chosen a suboptimal path. As the minimum number of moves was indicated, PD patients as well as healthy controls have most likely not planned ahead complete solutions but seemingly started instead to execute already after having found a partial solution path towards a first goal move, which in problems with suboptimal alternatives could have been also misleading. Thus, it rather seems that increased problem difficulty due to suboptimal alternatives might be mainly related to other processes such as, for instance, to successfully inhibit a premature selection of inappropriate moves (Carder, Handley, & Perfect, 2004). Future research should therefore address these issues in particular.

Taken together, systematic manipulations of TOL problem structure in the present study provided clear evidence that detection of planning deficits in PD

[8]A comparison of five-move problems with an unambiguous goal hierarchy and search depths of two intermediate moves across Parts I and II (P13 and P21, see Fig. 1-B and 1-C) allows to estimate the impact of suboptimal alternatives on planning performance. Results revealed a highly significant effect of suboptimal alternatives [$F(1,58)=90.48$, $p<.001$, $\eta^2=.609$] which was, however, entirely independent of group [$F(1,58)=1.19$, $p=.280$, $\eta^2=.020$] or any interactions with group [$F(1,58)=.18$, $p=.674$, $\eta^2=.003$].

patients is dependent on the cognitive demands of the specific problems employed in the task. Given the wide-spread use of the TOL and other related disc-transfer tasks as assessment tools in clinical and research contexts, more attention should be paid to the effects of problem structure.

Chapter 6 – Higher Order Language Functioning in Parkinson's disease

Abbreviations used in the text Chapter Six

1) **BDI-II** = Beck Depression Inventory; 2) **DRS-II** = Dementia Rating Scale-II; 3) **DSM-IV** = Diagnostic and Statistical Manual Fourth Edition; 4) **H&Y =** Hoehn and Yahr Staging Scale; 5) **ID/ED** = Inter Dimensional/Extra Dimensional Shift; 6) **MMSE =** Mini Mental Status Exam; 7) **NART** = National Adult Reading test 8) **PD** = Parkinson's disease; 9) **TLC-E** = Test of Language Competence Expanded Edition - Level 2; 10) **UPDRS** = Unified Parkinson's disease Rating Scale; 11) **WASI =** Wechsler Abbreviated Scale of Intelligence.

6 1 Overview

Language deficits in Parkinson's disease are traditionally associated with motor symptoms that affect both movement and speech. However, deficits in higher order language have been associated with PD, with speed of processing and working memory being suggested as mediating any deficits. Higher order language skills are necessary for everyday communication and enable the interpretation of covert meanings associated with inference and ambiguity. These processes rely on intact prefrontal functioning that enable individuals to respond quickly and appropriately to novel situations (McNamara & Durso, 2003; Pearce, McDonald, & Coltheart, 1998). However, there is considerable debate as to the exact nature of the relationship between higher order language and other cognitive process mediated by the prefrontal cortex. Currently little information exists as to whether any language deficits are a primary effect of the disorder or secondary to the cognitive deficits that commonly accompany PD. Therefore, the present study had two major aims: First, to examine higher-order language functioning in patients with PD without dementia; and second, to examine the degree to which any language deficits might be mediated by cognitive deficits associated with the pre-frontal cortex, including working memory, information processing speed and attention.

6.1.1 Difficulty with research in this area

Assessing skills that resemble those that are used in everyday communication is difficult in the confines of a structured testing setting. Only certain aspects of higher-order language can be assessed in a structured environment that is created during standardized neuropsychological testing, this study does not evaluate these deficits in an ecologically-valid way, that is, *in situ*. Additional or different aspects of

language than that tested may be impaired in actual conversational interactions which are often rapid and unpredictable.

6.2 Current Research

6.2.1 Manuscript 1 – Higher Order Language

This manuscript aimed to address the fifth objective of the thesis; the identification of the relative contribution of working memory and speed of processing on higher order language skills. Overall, PD patients were impaired on aspects of higher-order language, working memory and speed of mental processing. Measures of cognition were significantly correlated with language functioning. Path analyses revealed that deficits in higher order language functioning were mediated by verbal working memory and speed of information processing. Regression analyses found that speed of information processing was a stronger determiner of language performance than verbal working memory. We found that higher-order language deficits are not a primary effect of PD, but can be explained in terms of deficits in speed of information processing associated with the disease.

As a caveat to this manuscript, it is important to be aware that the particular analysis chosen has some disadvantages. Path analysis provides a mathematical way to test the hypothesized relationships between variables. The major advantage of using path analysis is that it permits the testing of hypothesized causal models (MacKinnon, Lockwood, Hoffman, West, & Sheets, 2002; Shrout & Bolger, 2002). However, these causal models are specified based on the theory, and better causal paths may be possible. Further, path analysis assumes that the relationships between the variables are linear, additive and causal. In reality these assumptions are often

violated (MacKinnon, Lockwood, Hoffman, West, & Sheets, 2002; Shrout & Bolger, 2002).

6.3 The Effect of Attention, Working Memory and Speed of Information Processing on Higher Order Language Functioning in Parkinson's disease

(In review Journal of Brain and Language)

6.3.1 Abstract

Parkinson's disease (PD) is traditionally associated with motor symptoms that affect both movement and speech. However, impairments in cognition and aspects of higher-order language functioning may also accompany this disorder. The present study investigated whether higher order language deficits in PD represented a primary deficit or were a secondary effect of deficits in cognition. Forty patients with PD were compared to age and IQ-matched controls on measures of higher- order language functioning using the Test of Language Competence- Expanded (TLC-E). Measures of cognitive ability that were potentially related to higher order language, including working memory, speed of mental processing and attention, were also obtained. Overall, PD patients were impaired on aspects of higher-order language, working memory and speed of mental processing. Measures of cognition were significantly correlated with language functioning. Path analyses revealed that deficits in higher order language functioning were mediated by verbal working memory and speed of information processing. Regression analyses found that speed of information processing was a stronger determiner of language performance than verbal working memory. Results suggest that higher-order language deficits are not a primary effect of PD, but can be explained in terms of deficits in speed of information processing associated with the disease.

6.3.2 Introduction

Parkinson's disease (PD) is a neurodegenerative disorder that largely affects the basal ganglia (Middleton & Strick, 2000a). Classic symptoms of this disorder are motor deficits and include rigidity, bradykinesia, tremor and postural instability (Vaughan & Hardie, 2002). It is thus not surprising that prior research on communication deficits in PD has generally studied those aspects of motor control which are related to speech production. Yet more recently there has been a growing awareness that PD is not only associated with impairments in language production, but also a range of cognitive deficits that may impact on language ability, including comprehension and effective verbal expression (Grossman, Carvell, Stern, Gollomp, & Hurtig, 1992; Owen, 2004a). Cognitive problems, similar to those associated with frontal lobe damage, are particularly implicated in the processing of complex information such as language (Royall et al., 2002). However, the exact nature of any deficits in higher order language functioning associated with PD is not well defined, and there is considerable controversy regarding the role of the prefrontal cortex in any language deficits that have previously been reported for these patients.

Specifically, such language-related deficits include reduced verbal fluency, difficulties with pragmatic language, processing of past tense verbs, and impairments in detecting and correcting syntax errors (McNamara & Durso, 2003; Monetta & Pell, 2007; Ullman, 2001). The most frequently-reported deficit involves the comprehension of sentences with complex or irregular grammatical structures (Bodis-Wollner & Jo, 2006; Grossman, 1999; Grossman et al., 1991; Grossman, Carvell, Stern, Gollomp, & Hurtig, 1992; Grossman et al., 2003; Lieberman, Friedman, & Feldman, 1990; McNamara, Krueger, O'Quin, Clark, & Durso, 1996). Impaired

sentence comprehension in PD has been associated with deficits in a number of tasks mediated by the prefrontal cortex including set switching, inhibition, working memory, attention and processing speed (Angwin, Chenery, Copland, Murdoch, & Silburn, 2005; Grossman et al., 2003; Grossman et al., 2002; Hochstadt, Nakano, Lieberman, & Friedman, 2006). Indeed, Grossman and colleagues (1992) reported that working memory and attention accounted for over 97% of the variance in complex sentence comprehension for PD patients. It is clear that a number of different skills, mediated by the prefrontal cortex, have been implicated with deficits in complex sentence comprehension. However, few studies have investigated impairments in higher-order language among PD patients and the impact of such deficits on everyday communication.

A range of higher-order language skills is necessary for everyday communication to enable the interpretation of covert meanings associated with inference and ambiguity. In general terms, language may be viewed as three distinct but interdependent aspects of communication: 1) content (semantics or meaning); 2) form (grammatical structure of sentences); and 3) use (social context of verbal interactions). Higher-order language requires intact functioning in all of these areas and is likely to rely on prefrontal skills that enable individuals to respond quickly and appropriately to novel situations. For example, pragmatic deficits, which refer to the use of language in context, including the ability to turn take and to respond with the appropriate quantity of relevant information, are seen following damage to the prefrontal cortex (McNamara & Durso, 2003; Pearce, McDonald, & Coltheart, 1998), and have also been found in PD patients. McNamara et al. (2003) examined pragmatic ability in 22 non-demented PD patients and reported significant deficits when compared to healthy controls, these deficits correlated with poorer performance

on tests of prefrontal ability. Lewis et al. (1998) compared the higher-order language abilities of 20 non-demented PD patients (all Hoehn and Yahr stage 3) compared to healthy controls. PD patients were significantly poorer at interpreting ambiguity, figurative language and sentence construction. Furthermore, patients with lower levels of general cognitive functioning were more impaired than other PD patients. However, their study did not examine the relationship between deficits in higher order language and different measures of prefrontal functioning.

It is evident from the existing literature that a range of cognitive and language deficits are associated with PD. However, there is currently little information as to whether the language deficits are a primary effect of PD, or secondary to the cognitive deficits associated with the disease. This question is particularly pertinent in terms of higher-order language functioning, which relies on a number of skills that are generally considered to be mediated by the pre-frontal cortex. Therefore, the present study had two major aims: First, to examine higher-order language functioning in patients with PD without dementia; and second, to examine the degree to which any language deficits might be mediated by cognitive deficits associated with the pre-frontal cortex, including working memory, information processing speed and attention.

6.3.3 Methods

This study received approval from the Upper South B Regional Ethics Committee. Parkinson's patients in the Canterbury region, who could be identified at the time of this study and had not been diagnosed with dementia, were invited by letter to participate. Participants were required to meet the following inclusion criteria: a) a diagnosis of idiopathic Parkinson's disease, confirmed by a specialist neurologist b) assessed at the Hoehn & Yahr stage I-IV; c) aged between 50 and 80 years; d) adequate or corrected hearing and vision (self report checked by examiner); e) stable on PD medication; f) English as the primary spoken language; g) no suspicion of dementia (MMSE ≥25). The following exclusion criteria were applied: a) currently involved in a therapeutic trial; b) a history of: i) moderate or severe head injury, ii) stroke or other neurological impairment, iii) other major medical illness , iv) significant psychiatric illness requiring hospitalization, v) major depressive episode in the previous 6 months; c) diagnosis of, or special education for, a learning disability, d) pre-morbid IQ estimated at <85 using National Adult Reading Test (NART); e) currently taking medications known to have a significant effect on Central Nervous System (other than medications prescribed for the control of PD symptoms) and f) Beck Depression Inventory–II score of >16.

Of the 115 letters that were mailed, 6/115 (5.2%) of individuals with PD could not participate due to illness, 6/115 (5.2%) were deceased, 8/115 (6.9%) declined, 34/115 (29.6%) did not respond, and 21/115 (18.3%) did not meet the inclusion/exclusion criteria. Forty participants with PD who met the exclusion/inclusion criteria were available to participate in the study. All patients

were on antiparkinsonian medication and were tested while on optimal levels of medication (self-report and examiner observation).

Controls:

Controls were recruited from a number of sources including a previously established data base, advertisements at local clubs (bowling, hiking and table tennis) and businesses. All controls were given a brief outline of the study on first phone contact. If they were still willing to participate, an information sheet was mailed to them. In addition to adequate or corrected hearing and vision (self report and checked by the examiner) and being aged between 50 to 80 years of age, the same exclusion criteria listed above also applied to the control group.

Procedure

Assessments were carried out at the University of Canterbury. Written informed consent was obtained from all participants at beginning of testing after the study had been explained.

Additional information pertinent to the inclusion/exclusion criteria was obtained from all participants using a semi-structured interview. PD patients also underwent a clinical assessment that included the Hoehn & Yahr staging and the Unified Parkinson's Disease Rating scale to assess motor impairment. All tests were conducted according to standardized procedures:

Clinical/Demographic Information

1) National Adult Reading Test (NART) (Nelson & Willison, 1991) was used to estimate pre-morbid IQ. This test is comprised of a list of 50 "irregular" words

printed in order of increasing difficulty. Words were scored 0 for incorrect and 1 for correct pronunciation (Lezak, 1995). Raw scores were converted to an estimated IQ score according to instructions in the manual (Nelson & Willison, 1991).

2) Vocabulary was assessed using a sub-test from the Wechsler Abbreviated Scale of Intelligence (WASI) (Wechsler, 1999). This test measured the participant's expressive language skills and consists of 42 orally presented words for which the participant provided a verbal description. Items were scored either 0 for an incorrect description, 1 for a partially correct description, or 2 for a correct description. Raw scores were converted to age corrected T-scores (mean of 50 and standard deviation of 10).

3) Beck Depression Inventory-II. (BDI-II) was used to assess mood and consisted of 21 items. Each question was rated 0-3 with higher scores indicating greater intensity of symptoms (Beck, Steer, & Brown, 1996). The BDI-II has been validated for use with PD patients, with a cut off of 16/17 being recommended for detecting the presence of depression (Leentjens, 2004).

4) The Mini Mental Status Exam (MMSE) provided information regarding current cognitive status of the participant and includes items that assess attention, orientation to time and place, short term memory and language. Scores range from 0-30, with lower scores indicating greater impairment. A variety of cut-offs have been suggested for this instrument, but scores below 23-24 have been reported as having high sensitivity and specificity for identifying individuals with dementia (O'Connor et al., 1989). Participants were included if they scored ≥25 (Folstein, Folstein, & McHugh, 1975).

5) To ensure that none of the patients included in the study met the criteria for dementia, the Dementia Rating scale (DRS-2) (Jurica, 2001) was used in addition to the MMSE. This scale consists of 36 tasks and five subscales. The five subscales provide information on specific abilities and include: 1. Attention; 2. Initiation/Preservation; 3. Construction ability; 4. Conceptualization; and 5. Memory. Based on normative data, raw scores from each subscale were summed to provide an overall score (ranging from 0-144 with higher scores indicating better performance) A DRS-II score of 130 has previously been validated as appropriate for PD patients (Brown et al., 1999). However, Green et al. (2002) noted that this may exclude some patients due to motor deficits. Therefore, patients with a total raw score of <120 were excluded and those with raw scores between 120 and 130 were further assessed for dementia by a registered clinical psychologist using the Diagnostic and Statistical Manual of Mental Disorders-IV (DSM-IV) criteria. Two patients scored below 130, but neither patient met the DSM-IV criteria for dementia. A combined scaled score adjusted for age and education was then generated using a regression formula provided in the administration manual is used for comparisons between the groups (Jurica, 2001).

Two additional measures were used for patients with PD to provide information regarding motor impairment.

6) Unified Parkinson's Disease Rating Scale (UPDRS) (Fahn & Elton, 1987) is a 42 item test covering 4 areas. Section one assesses mentation, behavior and mood, section two assesses activities of daily living, section three severity of motor symptoms and section four complications of therapy. For this study scores

from the motor section were used to provide information regarding severity of motor problems.

7) The Hoehn and Yahr (H&Y) was used to rate the stage of the disease (Hoehn & Yahr, 1967). A numeric rating of 0-5 is used to represent increasing severity of symptoms, where 0 indicates no sign of the disease and 5 indicates that the patient is wheel chair bound or bedridden unless aided. The modified version of this scale was used, which provides increments of 0.5 in the midranges.

Language and Cognitive assessment:

1. **Test of Language Competence- Expanded Edition (TLC-E):** The TLC-E Level two was used to assess higher order language functioning. This test is comprised of four sub-tests, three related to comprehension and one to language formulation. Explicit scoring instructions are provided in the test manual (Wig & Secord, 1989). Five scores were generated from this test: A total score (maximum = 189), and four subtest scores that corresponded to the following areas of language competence:

- Ambiguous Sentences: assessed the participant's ability to recognize lexical and structural ambiguities of a sentence. Participants were orally presented a sentence that had two alternative meanings. The ambiguous sentence was then displayed in print. For example, "I saw the girl take his picture". Participants were then asked to provide two correct meanings for the sentence. A total of 15 sentences were presented, two trial sentences and 13 test sentences. A score of 0 was given for no correct responses, 1 for one correct response, and 3 if the participant correctly identified both correct responses. Possible scores ranged from 0-39.

- Listening Comprehension (making inferences). The objective of this subtest was to assess the participants' ability to identify inferences in a series of short paragraphs. Participants were first read a scenario that was displayed in print. For example, "Eric had wanted a moped for the longest time. He sure was grateful for his Uncle Fred. Question: Eric was grateful for Uncle Fred because…" Participants were then read four statements, provided in print at the bottom of the page, and asked to select two plausible inferences for the scenario. A total of 13 sentences were presented in this manner (one trial sentence and 12 test sentences). A score of 0 was given for no correct responses, 1 for one correct response, and 3 if the participant correctly identified both correct responses. Possible scores ranged from 0-36.
- Oral Expression (recreating sentences). This subtest was used to evaluate the ability to formulate a grammatically complete sentence incorporating three key words. Participants were presented with a picture of a scene and read a sentence. At the top of the picture were three words. The participant was required to create an appropriate sentence incorporating all three words. Two trial sentences and 13 test sentences were presented. All responses are recorded verbatim and are scored for inclusion of target words, 0 for one or no target words, 1 for any two words, and 3 points for all three words. Sentences were also scored in terms semantic, syntactic and pragmatic accuracy. Intact sentences were given a score of 3 points, sentences with minor deviations 1 point and 0 points for major deviations which result in nonsensical, "bizarre", or fragmented sentences. Possible scores ranged from 0-78.
- Figurative Language: This subtest is comprised of two parts and is designed to assess the ability to interpret metaphoric expressions. In task A, participants

were verbally presented with a situation, e.g., "A boy talking about his girlfriend" and a figurative expression related to the situation "she is easily crushed". Both the description of the situation and the figurative expression were also presented in print. Participants were then asked to provide an interpretation for the figurative expression which was recorded verbatim. In task B, they were asked to match the figurative expression to one of four explanations. The situation description, figurative expression and the four explanations were all presented in print. The test consists of one trial and 12 test items. A score of 0 is given if the participant is unable to give an accurate interpretation or select the correct matching expression. A score of 1 is given if the participant could give either an accurate interpretation or select the correct matching expression and 3 if they complete both task A and B correctly. For each of the subtests, a discontinue rule of failure to respond to three consecutive items is used. Possible scores range from 0-36.

2. Attention: This skill was assessed using the sub-test of Digits Forward from the Wechsler Memory Scale-III (WMS-III) (Wechsler, 1997), in which participants were required to repeat an increasing string of verbally-presented digits (2-9 items). Two trials were presented for each level of difficulty. The test was discontinued if a participant was unable to correctly answer both of the trials at any given level. Raw scores were then age adjusted using the procedures set out in the manual [mean 10, standard deviation, 3].

3. Working Memory: The Daneman and Carpenter Reading Span test (Daneman & Carpenter, 1980) was used to assess verbal working memory (Waters & Caplan, 1996a). This test involved the presentation of sets of 2 to 6 sentences, each consisting of 8 to 13 words. Testing began with sequences of two

sentences with three trials. Participants were asked to read the first sentence out loud, judge the veracity of the statement, and remember the last word in the sentence. They then read the second sentence out loud, again judged the veracity of the statement and remembered the last word. At the end of the trial, which was signified by a blank card, the participant was asked to recall as many of the last words as possible, but not starting with the last word presented unless that was the only word they could remember. The participant then moved on to sequences of three, four, five and six sentences. Each level of complexity had three trials, with a total of 60 sentences being presented. The reading span was the maximum number of words remembered with over 65% accuracy (two out of three trials correctly recalled). The test was discontinued if a participant is unable to remember the last word from any of the sentences in a trial set.

4. **Speed of Mental Processing:** Word naming and Color naming from the Delis Kaplan Executive Function System (D-KEFS) (Delis, Kaplan, & Kramer, 2001) were used to assess this skill. For the color naming portion of this test, participants were presented with a page with rows of colored patches or words that they were required to name or read. For both conditions, they were asked to name the colors or read the words as quickly as possible without skipping any or making any mistakes. Time taken to identify the colored patches or words was recorded. Raw scores were then converted to age-adjusted scores with a mean 10, standard deviation, 3, as specified in the manual. Scores for color naming and word reading were then averaged to provide a single score for speed of mental processing.

6.3.4 Data analyses

Differences in demographic and clinical characteristics were examined using *t* tests and χ^2 as appropriate. *t* tests were also used to compare PD patients and matched controls on measures of language, working memory, speed of mental processing and attention. Total scores for language and each of the sub-tests were then converted to *z*-scores using the control mean and standard deviation so that comparisons could be made across these measures. Pearson correlations were employed to assess the association between language, working memory, speed of mental processing, and attention. Separate path analysis models were then used to test whether the relationship between PD and deficits in higher order language could be explained by working memory, speed of mental processing, and attention as mediating variables (Sobel's *z*). Finally, multiple regressions were used to assess the influence of measures of working memory and speed of mental processing on higher-order language functioning.

6.3.5 Results

Demographic and clinical characteristics

Comparisons between patients with PD and their healthy controls on clinical and demographic characteristics are shown in Table 55. Each of the 40 PD patients, included in the main study, was matched as closely as possible to a healthy control in terms of age and pre-morbid IQ using the NART. Matching was confirmed by *t* tests (IQ: $t = 0.94$, $df = 78$, $p > .30$; and age: $t = 0.31$ $df = 78$, $p > .75$).

Patients with PD had significantly lower MMSE scores and were more likely to endorse symptoms associated with low mood (see Table 55). Also, there were

significantly more males in the PD group (PD 26/40 [65%] v Control 13/40 [32.5%]) ($\chi^2(df = 1) = 8.46$, $p < .01$). Motor scores for patients with PD varied from mild to severe as measured by the H&Y (see Table 55).

Table 55: Clinical and demographic characterstics, Parkinson's disease group versus controls.

	Parkinson's disease (n=40)			Control Group (n=40)				
	Mean	SD	Range	Mean	SD	Range	t-value	p-level
NART[1]	109.05	[10.13]	87-131	111.20	[10.30]	90-128	0.94	>0.30
Education (yrs)[2]	13.94	[2.56]	11-22	13.76	[2.57]	8-20	-0.30	>0.75
Vocubulary	56.60	[7.98]	39 - 70	59.13	[7.69]	43 - 73	1.44	>0.15
Age	66.15	[6.65]	52-77	66.58	[5.47]	52-76	0.31	>0.75
MMSE[3]	28.65	[1.42]	25-30	29.58	[0.71]	28-30	3.67	**<0.001**
BDI-II[4]	7.59	[4.34]	0-16	4.13	[3.39]	0-15	-3.96	**<0.001**
PD Onset[5]	6.49	[4.35]	0.25-23					
UPDRS[6]	28.46	[9.49]	13-49					
H&Y Stage[7]	1 (n=8)	1.5 (n=6)	2 (n=7)	2.5 (n=10)	3 (n=7)	4 (n=2)		

[1]National Adult Reading Test, [2]Total number of years formal education, [3]Mini Mental Status Exam, [4]Beck Depression Inventory, [5]Number of years since diagnosis of Parkinson's disease, [6]Unified Parkinson's Disease Rating Scale (motor score component); [7] Hoehn and Yahr.

Results for tests of higher-order language functioning are shown in Table 56. There were significant differences between PD patients and matched controls. PD patients performed more poorly in terms of their overall TCL-E score and for three out of the four subtests. Deficits were also evident for tests of speed of mental processing and working memory, as measured by the combined color and word identification task and the Daneman and Carpenter Reading span task, respectively. However, there was no significant difference for measures of attention as assessed by the digits forward task or for ability to interpret ambiguous sentences.

Table 56: Comparisons between Parkinson's disease group and matched controls on measures of Language Functioning, Information Processing Speed, Working Memory and Attention.

	PD Patients	Controls	*t*	*p*
TLC-E Total[1]	155.95 (19.12)	167.28 (16.22)	2.86	**<0.01**
Subtests:				
Ambiguous Sentence	31.18 (6.47)	32.35 (5.63)	0.87	>0.35
Making Inferences	25.73 (4.87)	29.73 (4.64)	3.76	**<0.001**
Oral Expression	68.70 (8.22)	72.78 (6.07	2.52	**<0.02**
Figurative Language	30.25 (5.48)	33.10 (3.79)	2.71	**<0.01**
Information Processing Speed	9.66 (1.87)	11.34 (1.47)	4.46	**<0.0001**
Reading Span Task	1.66 (0.57)	2.46 (0.67)	5.73	**<0.0001**
Digits Forward	10.23 (2.13)	10.95 (2.25)	1.48	>0.10

[1] Test of Language Competence – Expanded, total score.

For descriptive purposes and to enable comparison between the different sub-tests, raw scores were converted to z-scores using the control mean and standard deviation. Figure 21 displays the comparison between PD and their matched controls using z-scores for total TCL-E score and each of the four sub-tests. Parkinson's patients did not differ from matched controls in terms of their understanding of sentences that contained ambiguity. However, for three of the four sub-tests, PD patients were performing between 0.67-0.82 SD below the mean of the matched controls.

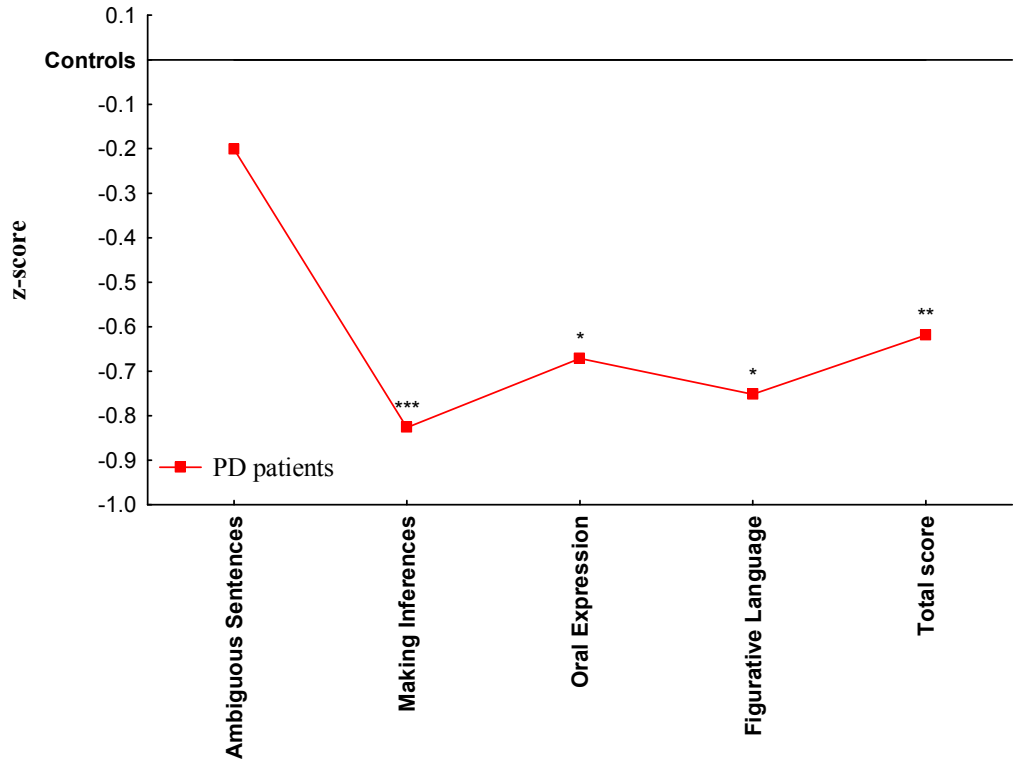


Figure 21: Comparisons between the matched control group and Parkinson's disease patients for different aspects of higher order language using the Test of Language Competence – Expanded.

Note: *p<.05; **p<.01; ***p<.001.

Table 57: Correlations between measures of Language Functioning, Speed of Processing, Working Memory and Attention for the combined Parkinson's disease and Control group (n=80).

	TCL-E Total	Ambiguous Sentences	Making Inferences	Oral Expression	Figurative Language	Processing Speed	Reading Span Task	Digits Forward
TCL-E Total								
Ambiguous Sentences	0.72***							
Making Inferences	0.73***	0.39***						
Oral Expression	0.78***	0.42***	0.42**					
Figurative Language	0.82***	0.45***	0.60***	0.51***				
Processing Speed	0.51***	0.27*	0.54***	0.48***	0.42***			
Reading Span Task	0.36***	0.26*	0.35**	0.22	0.40***	0.39***		
Digits Forward	0.40***	0.25*	0.26*	0.39***	0.35**	0.35**	0.24*	
PD vs Control	-0.31**	-0.10	-0.40***	-0.28*	-0.29**	-0.45***	-0.54***	-0.17

Note: *p<.05;**p<.01; ***p<.001

Because we were interested in the relationship between language performance and cognitive processes, we first examined the correlations between language functioning and speed of processing, working memory, and attention. Table 57 shows correlations for the combined sample (i.e., PD patients and controls). Not surprisingly, there were significant positive correlations between all each of the different measures of cognition and higher order language functioning. Significant negative correlations were also found between disease state (i.e., PD vs Control) and measures of cognition and higher-language functioning, confirming the deficits shown by PD patients in Figure 21 and Table 56.

Next a series of path analyses were conducted to determine whether the language deficits observed in the PD patients might be a secondary effect of deficits in cognitive functioning. Specifically, we tested whether working memory, information processing speed, and attention might mediate the relationship between disease state and higher-order language functioning evidenced in Table 57. Because the TCL-E subtests were highly correlated, we used the total score as our measure of higher-order language functioning.

Four basic steps were followed in the models described here (Shrout & Bolger, 2002). First, the direct path in which the independent variable (in this case disease state) caused a change in another dependent variable (in this case higher order language) was calculated (represented by the solid arc in Figures 22 and 23). We then tested the relationship between disease state and a potential mediating variable (attention, information processing speed and working memory). Next, the relationship between the proposed mediating variable and higher order language was assessed. Finally, we calculated the change in the relationship between disease state

and higher order language when the mediator was included. The resulting effect is the indirect path and is signified by a dotted line in Figures 22 and 23. To see whether the pattern of results reflected a significant change we used Sobel's *z*-test (Baron & Kenny, 1986).

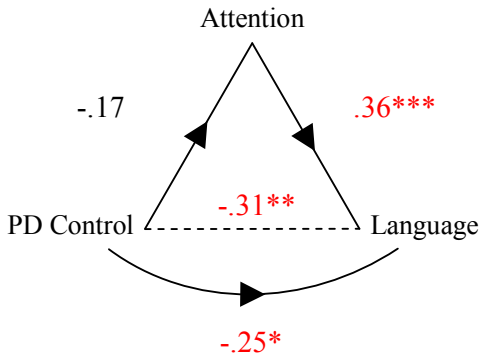


Figure 22: Path diagram where the intervening variable is Attention.

As can be seen in Figure 22, there was no significant association between PD disease state and attention. Further, although performance on measures of attention were significantly associated with language performance, there was no evidence of a significant mediating effect (Sobel's z =1.37, p>0.15) and the relationship between disease state and higher order language remained significant even after attention was controlled for (see Table 53 for beta weights).

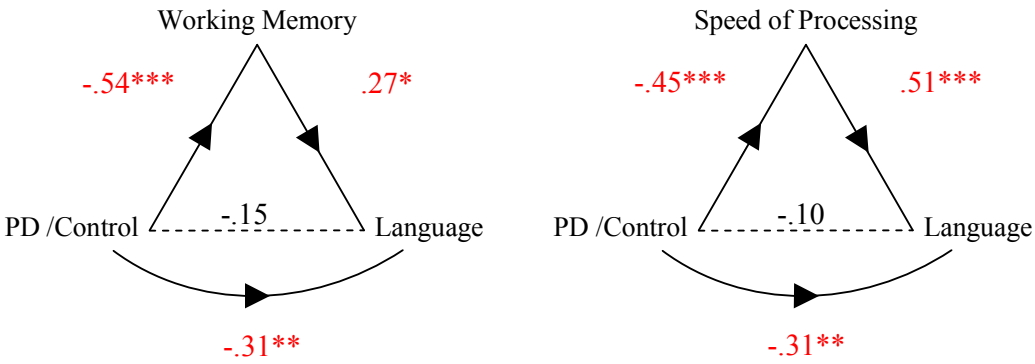


Figure 23: Path diagram where the intervening variable is Working Memory and separately Information Processing Speed.

Figure 23 shows that there was a significant change in the relationship between disease state and higher order language functioning with the inclusion of either working memory or information processing speed as a mediator (see Table 58 for full results). For both these models, the indirect pathway between disease state and higher order language functioning was no longer significant when the mediating variable was included, and the drop in association between the direct and indirect pathways was significant (Sobel's $z = 2.30$, $p < 0.05$ and $z = 3.1$, $p < 0.01$ for working memory and information processing speed respectively). Thus, results of the path analyses suggest that both working memory and speed of processing, but not attention, can explain the deficits in higher-order language functioning shown by the PD patients.

Table 58: Regression coefficients for mediating variables.[9]

Variable	*β*	*t*	*β*	*t*	*β*	*t*
	Step 1 (criterion: Lang)		Step 2 (criterion: PS)		Step 3 (criterion: Lang)	
Group	-0.31	-2.86**	-0.45	-4.46***	-0.10	-0.88 *ns*
Information Processing Speed (PS)					0.47**	4.32
			Step 2 (criterion: WM)		Step 3 (criterion: Lang)	
Group			-0.54	-5.73***	-0.16	-1.27*ns*
Working Memory (WM)					0.27	2.16*
			Step 2 (criterion: ATT)		Step 3 (criterion: Lang)	
Group			-0.17	-1.48*ns*	-0.25	-2.43*
Attention (ATT)					0.36	3.57***

Because measures of working memory and processing speed were correlated (see Table 57), we conducted a final series of regressions to test whether one of these variables might be primarily responsible for the language deficits associated with PD. For these analyses, group (PD vs control) and verbal working memory (or information processing speed) was entered at the first step, and speed of processing (or verbal working memory) was entered at the second step. When group and verbal working memory were entered in the first step, information processing speed was significantly related to the TCL-E (β=0.44, R^2 change =0.15, p<0.001). When information processing speed and group were entered on the first step, verbal working memory was not significantly related to the TCL-E (β=0.18, R^2 change =0.02, p<0.15). These results suggest that information processing speed is a stronger determiner of performance on the TCL-E than verbal working memory, and hence that the higher-

[9] Full details for this analysis are contained in the appendix XXIX.

order language deficits associated with PD are best understood as being mediated by deficits in processing speed.

6.3.6 Discussion

The goal of this study was to assess higher order language functioning in patients with PD compared to healthy older adults, and to examine the degree to which deficits that were observed could be explained by processes associated with the pre–frontal cortex. These processes included working memory, speed of information processing and attention. Patients with PD performed significantly more poorly on higher order language tasks than healthy controls. Performance on higher order language tasks were significantly correlated with information processing speed, verbal working memory and attention. These three pre-frontal skills accounted for 13% to 26% of the variance on the TCL-E. Whereas path analyses indicated that both verbal working memory and information processing speed mediated the relationship between disease status and higher-order language functioning, multiple regressions confirmed that information processing speed was a stronger determiner of language performance than verbal working memory. Overall, these results suggest that the higher order language deficits in PD are secondary to deficits in information processing speed, for which the pre-frontal cortex plays a pre-eminent role.

The comparisons between PD patients and matched controls in the present study are consistent with previous studies, which have documented deficits in speed of information processing and working memory in PD patients (Berry, Nicolson, Foster, Behrmann, & Sagar, 1999; Lewis et al., 2003; Lewis, Dove, Robbins, Barker, & Owen, 2003; Lewis, Slabosz, Robbins, Barker, & Owen, 2005; Pillon et al., 1989). Further, PD patients have consistently been reported as experiencing difficulty in

different components of language, particularly understanding complex sentences (Grossman et al., 2002; Hochstadt, Nakano, Lieberman, & Friedman, 2006). Deficits in working memory and speed of processing have previously been reported as affecting the accuracy of patients with PD with regard to understanding of complex sentences (Grossman et al., 2002; Hochstadt, Nakano, Lieberman, & Friedman, 2006).

Although relatively few studies have investigated outcomes for PD patients in terms of higher-order language functioning, Lewis et al. (1998) found that patients with PD exhibited deficits in understanding ambiguous and figurative language. In this study patients did not show any difficulties in interpreting ambiguous sentences. However, patient characteristics may account for this apparent discrepancy. Whereas Lewis et al.'s (1998) patients were assessed at H&Y stage III, the present study included patients across a wider range of severity (H&Y stage I-IV) to increase the generalizability of the findings.

Attentional skills are required for performance of the skills associated with higher order language. However, because PD patients have consistently been reported as having preserved attentional skills (Boller, Marcie, Starkstein, & Traykov, 1998; Bradley, Welch, & Dick, 1989; Cooper, Sagar, Jordan, Harvey, & Sullivan, 1991) it is not surprising that attention was not predictive of any deficits of higher order language.

Results suggest that skills mediated by the pre-frontal cortex play a primary role in higher-order language. Higher-order language functioning required in everyday communication is complex, with a considerable degree of novelty. It would be expected that these types of language interactions would rely more heavily on

skills mediated by the prefrontal cortex because of their demands on attention, working memory and speed of information processing.

The method of assessment used here enabled an examination skills which more closely resemble those that are used in everyday communication and their relationship with skills associated with the prefrontal cortex. Nonetheless, it is pertinent to consider the limitations of this study. Only non-demented patients with no illnesses apart from PD were included. It is likely that higher order language deficits would be more severe in patients with greater cognitive decline. Further, although we endeavoured to obtain a representative sample patients were self-selected.

Higher-order language used in everyday communication requires the ability to understand meanings which extend beyond the actual words spoken. Understanding of ambiguity and inference is also required. Even subtle deficits in these areas of language may serve to increase isolation of PD patients from normal social interaction intensifying their reduced quality of life (Miller, Noble, Jones, & Burn, 2006). It is also likely that these types of difficulties may cause frustration for caregivers who may not understand the changes in comprehension and interpretation that are occurring for the patient. Understanding the exact nature of cognitive deficits, or intact skills, which could facilitate learning, could potentially provide a means of intervention to ease any language problems. For example, education for professionals and caregivers regarding how to present information in an appropriate way to enhance communication could ease the frustration of caring for an individual who has difficulty communicating. Patients could be instructed in the use of strategies to clarify misunderstandings. Further, because effective communication appears to be

linked with intact cognition, professionals could screen for cognitive decline as a marker for communication problems and take steps to intervene early in the disease process.

Chapter 7 – Contribution to the field of Parkinson's disease

7.1 Opening Discussion

Parkinson's disease is one of the most common neurological disorders affecting people over the age of 50 years (de Rijk et al., 1997; Twelves, Perkins, & Counsell, 2003). Historically, research in this field has focused on the overt motor impairments that characterise this disorder with tremor, rigidity, postural instability and bradykensia being the hallmark features (Braak & Braak, 2000). While the etiology of PD remains unknown, neuropathalogical findings indicate that the loss of dopamine containing neurons in the substantia nigra and the nigrostriatal tract are primarily responsible for the characteristic motor symptoms (Braak & Braak, 2000). More recently, it has been recognised that in addition to the motor symptoms that accompany this disorder, cognitive and neuropsychiatric disturbances may also be a feature of the disease process (Brown & Marsden, 1990; Marsh, 2000). However, the exact nature of any cognitive or neuropsychiatric problems remains undetermined.

The finding that cognitive and neuropsychiatric disturbances are frequently co-morbid with the motor problem is not surprising. Contemporary models of the basal ganglia suggest that these structures are involved in at least 5 parallel loops within the cerebral cortex. Two of these loops are involved in motor functioning, with the remaining three loops implicated in cognition and behaviour (Alexander & Crutcher, 1990; Alexander, DeLong, & Strick, 1986). Deficits associated with PD are thought to result from dysfunction in these loops, secondary to the depletion of dopamine containing neurons in the substantia nigra that project to the basal ganglia. The resultant degeneration in the fronto-striatal circuits is associated with a wide range of problems for individuals' with PD, many of which are poorly defined.

Figure 24 below offers a way to conceptualise the relatively complex array of problems that may impact on the functional profile for individuals with PD.

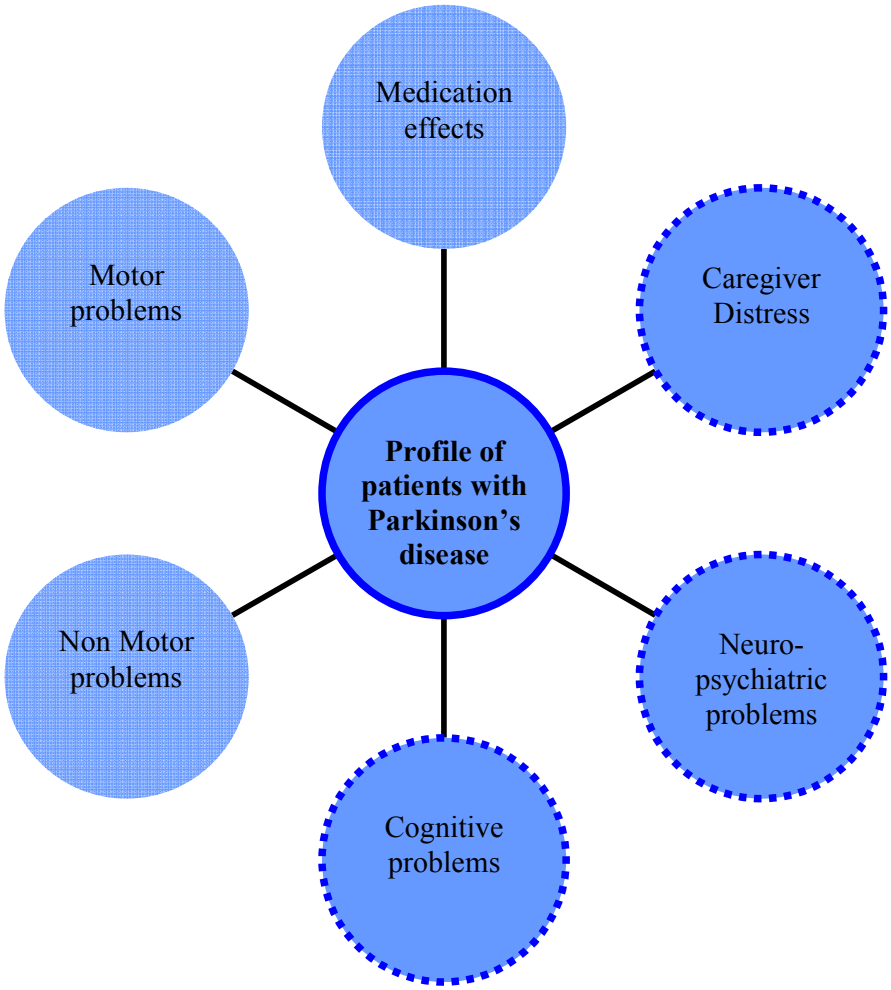


Figure 24: A schematic representation of the issues that influence the functional profile of patients with Parkinson's disease.

(Circles with the dark boarders indicate the issues addressed in this thesis).

Both physical (i.e. motor functioning, non-motor functioning and medications effects), and non physical problems (i.e. cognitive and neuropsyciatric problems and caregiver distress), contribute to this profile. While there is abundant literature

regarding the most common motor symptoms and effective assessment and treatment protocols for ameliorating these, there is still considerable debate regarding the typical cognitive and neuropsychiatric profile. This in turn results in a lack of a consensus regarding the appropriate assessment for any cognitive and neuropsychiatric problems that might accompany this disorder.

The general aims[10] of this thesis were:

a) To contribute to the understanding of neuropsychiatric problems for PD patients.

b) To contribute to the understanding of cognitive deficits in PD by:

    i) Defining the aspects of executive function that are impaired or spared.

    ii) Exploring whether sub-groups of people with PD could be identified based on their cognitive profile. It was specifically intended to identify people with PD who could be considered as suffering from MCI.

    iii) Examining aspects of planning ability in PD patients.

    iv) Examining deficits in complex language.

c) To identify a discrete battery of tests that could be used to identify patients with PD who might be experiencing MCI.

[10] A full description of the objectives for the thesis can be found in Chapter One, pages 64-66.

7.2 (A) Neuropsychiatric problems

Although neuropsychiatric problems have previously received little attention in the literature, there is increasing recognition that they are frequently co-morbid with motor problems associated with PD (Shulman, Taback, Bean, & Weiner, 2001). Further, these neuropsychiatric problems can have a significant impact on the quality of life for PD patients and in some cases may be more disruptive than the motor symptoms (Fernandez, Tabamo, David, & Friedman, 2001). Therefore, to contribute to the understanding of neuropsychiatric problems for PD patients, this thesis assessed a range of possible problems (including depression, anxiety, fatigue, apathy, sleep difficulties and hallucinations) in order to establish a likely profile for patients with PD without dementia. Moreover, the relationship between these neuropsychiatric problems and quality of life was also examined. Further, as depression is one of the most frequently reported neuropsychiatric problems, commonly used scales of depression were assessed to identify which was most sensitive to symptoms consistent with low mood or depression in PD.

Collateral information from a significant-other[11] regarding the presence of these problems was also collected to determine whether these two sources of information were interchangeable. As neuropsychiatric problems have been found to impact on the caregivers' ability to cope, the levels of distress that significant others were experiencing and the relationship of this distress to problems experienced by the PD patient, were assessed.

[11] The significant other was a person volunteered by the patient who knew them well. In most cases this was a spouse.

7.2.1 Overview of Results

Overall, neuropsychiatric problems were common for patients with PD, with over 70% of patients experiencing at least one problem. Fatigue, depression, apathy and sleep difficulties were the most commonly reported problems, whereas symptoms consistent with anxiety and the presence of hallucinations were relatively less common. Neuropsychiatric problems were associated with non-tremor scores but not tremor scores, age, gender or disease duration. Most importantly, in addition to motor deficits, neuropsychiatric problems contributed to a reduced quality of life for individuals with PD.

The level of agreement regarding the presence of neuropsychiatric problems between significant others and patients with PD was low. A maximum agreement level of approximately 40% was found for the presence of apathy, with a low of 7.7% agreement for the reported presence of symptoms consistent with anxiety. These results suggest that the ratings of significant others and patients cannot be treated as interchangeable. Interestingly, levels of stress reported by the significant-other were influenced by their perception of the presence of neuropsychiatric problems in the patient, not just the presence of these problems.

In terms of the most sensitive screening measure of depression, there was a high level of agreement between the BDI-II and the GDS. By contrast, the HADS identified significantly fewer of the patients as having possible or probable depression. Given the prevalence of depression among patients with PD, it is recommended that either the BDI-II or the GDS be used as a routine screen for depression. While some have argued that the BDI-II may identify too many false positives, this scale has the important advantage of being consistent with the criteria

for a major depressive episode outlined in the DSM-IV. Moreover, all self-report scales used for the detection of symptoms consistent with depression, are screening measures. Therefore, patients identified as "at risk" would still require screening by a qualified clinician for a diagnosis to be made, negating the disadvantage of a high level of false positives.

7.2.2 Summary

In summary, as neuropsychiatric problems are frequent and affect quality of life for many patients with PD, patients should be routinely screened for these problems. Depression is one of the most common neuropsychiatric problems associated with PD and that both the BDI-II and GDS were equally sensitive at detecting symptoms of low mood or depression for this patient group. However, the HADS or the UPDRS alone were not sensitive and had unacceptably high levels of false negatives.

Significant-other reports provide valuable information regarding their own perception of the patient's problems. However, significant-other reports of neuropsychiatric problems cannot be considered interchangeable with self-reports as they are likely influenced by the significant-others own levels of stress which may be unrelated to the patient's problems. Research suggests that it is important to monitor significant- other stress as it may signal increased difficulties coping with the needs of a patient with PD. Moreover caregiver-stress maybe manageable with appropriate intervention or education, providing potential benefits in terms of improved quality of life for both the carer and the patient.

7.3 (B) Cognitive deficits in PD

Cognitive deficits commonly accompany PD, even in the absence of dementia. However, there is still considerable controversy regarding the exact profile of deficits associated with this disorder (Brown & Marsden, 1990; Lewis et al., 2005). To contribute to the understanding of cognitive deficits that accompany PD in the absence of dementia, a comprehensive assessment across multiple domains (including, memory/learning, language, planning, visuospatial ability, working memory, problem solving, executive function, attention, and speed of processing) was conducted. This project placed a particular emphasis on tests that were sensitive to executive dysfunction and its sub-components. While deficits in individual aspects of executive functions have frequently been reported, there is little information regarding which aspects are impaired or spared for patients with PD.

As part of examining the cognitive profile for PD, this project also examined the possibility that different sub-groups of patients might exist that were identifiable by their cognitive deficits. This aspect of the research was particularly aimed at investigating areas of cognitive decline that might signal a period of decline consistent with preclinical dementia or "PD-MCI".

7.3.1 Overview of Results

A major contribution of this research was that it assessed a single group of patients on tests that covered a broad range of cognitive domains in order to identify a cognitive profile for PD patients. Evidence of impaired performance across different aspects of executive functioning and its sub-components (working memory, problem solving, planning and speed of processing) were found. Deficits in visuospatial functioning, independent of executive functioning, were also apparent. Interestingly,

patients with PD did not show a global decline on measures of executive functioning and there was evidence of relative sparing on most measures of planning and problem solving.

In the initial analysis for the project, evidence for planning deficits was at best weak. The only task where impairment was found was for a version of the Tower of London task. Furthermore, there was no sign of impairment for the Tower of Hanoi task, often used interchangeably with the Tower of London task as a measure of planning ability. It was hoped that the differences between these tasks would lead to a greater understanding of planning ability in PD patients.

Therefore, the relative sensitivity of these two widely used measures of planning ability was investigated. It was found that there was only a small percentage of shared variance between the two tasks. Moreover, the performance relied on different cognitive processes, and while performance on the Tower of London was dependent on inhibition and spatial working memory, performance on the Tower of Hanoi was dependent on intact spatial working memory. These results suggested that neither of the commonly used tower tasks were particularly good for detecting planning deficits per se. Therefore, a new tower task was designed to systematically manipulate problem complexity to more accurately tap into the skills required for planning. The results indicated that planning performance was generally intact, with impairments being evident only when the requirements of the task became more effortful.

As part of the investigation into cognitive deficits in PD, this thesis also investigated whether higher order language deficits represented a primary deficit or were a secondary effect to deficits in cognition. Overall, PD patients showed impairments on aspects of higher-order language, working memory and speed of

mental processing. Measures of cognition were significantly correlated with language functioning. Further, analysis revealed that the deficits in higher order language were mediated by verbal working memory and speed of information processing, with speed of information processing being a stronger determiner of performance. It was therefore concluded that higher-order language deficits were not a primary effect of PD, but could be explained in terms of deficits in speed of information processing associated with the disease.

All the initial analyses regarding cognitive performance (including higher order language and planning ability) were conducted comparing the patients with PD to matched healthy controls. However, it was evident that the patients varied greatly with regard to their cognitive performance. Moreover, this variance was not reliably associated with demographic or clinical characteristics.

To address the issues outline above, an investigation into whether sub-groups of PD patients could be detected that differed in terms their cognitive performance was undertaken. Sub-groups of PD patients were assessed in terms of between-group differences and also in comparison to individually-matched healthy controls in terms of their cognitive performance and ability to conduct activities of daily living. Three sub-groups of patients were identified that formed a continuum of cognitive impairment from mild to severe. Compared to their controls, one sub-group showed no or minimal cognitive impairment (PD-NCI), a second group showed a more variable pattern of severe and mild impairments (PD-UCI), and a third group had evidence of severe cognitive impairments across most of the cognitive domains tested. This latter group was labelled PD-Mild Cognitive Impairment (PD-MCI). The PD-UCI and PD-MCI groups were also significantly different from their controls with

respect to their ability to carry out functional activities of everyday living. Results confirm that patients with PD are heterogeneous with regard to their cognitive presentation. Further, the severity of cognitive deficits was not associated with other clinical and demographic characteristics such as motor impairments, age or disease duration. Patients were followed-up at one year (time 2) and results were consistent with time one.

7.3.2 Summary

In this study we found evidence of impairment for a number of areas of cognitive performance including working memory, verbal fluency, response inhibition and problem solving. However, there was limited evidence for deficits in the domains of attention, or planning. Further investigation indicated that planning deficits were present, but only when the task became more effortful. Deficits in aspects of language functioning were apparent, but these were secondary to other aspects of cognitive functioning i.e., speed of processing and working memory, with speed of processing being a stronger determiner of performance.

From our initial analysis it was evident that not all patients with PD were showing evidence of cognitive impairment. Indeed, three sub-groups of patients were identified that formed a continuum of cognitive impairment from mild to severe. These three groups also differed significantly from their controls with respect to their ability to carry out functional activities of everyday living. Severity of cognitive deficits was not associated with other clinical and demographic characteristics such as motor impairments, age or disease duration. Results from the one year follow-up confirmed the initial findings.

7.4 (C) Identification of a discrete battery of tests that could be used to identify patients with PD who might be experiencing MCI

7.4.1 Summary

The concept of PD-MCI provides a useful way of viewing cognitive decline in PD and could be used to guide appropriate treatment interventions. Unfortunately, there is currently no generally agreed on set of tests to evaluate potential cognitive and neuropsychiatric problems for patients with PD. Therefore, one aim of this study was to develop a discrete group of non-invasive tests that would have direct clinical application. Based on our findings at time one and the preliminary findings of time two, we were able to develop a brief battery of tests. The suggested test battery would provide comprehensive information regarding current cognitive and neuropsychiatric and motor status, and would be sufficiently brief to be incorporated as part of a routine follow-up procedure.

7.5 Future directions

An overall theme of this thesis has been to identify cognitive and neuropsychiatric strengths and deficits in people with PD. As part of this, the combination of measures most sensitive and appropriate for detecting the onset of cognitive decline (taking into account the possible neuropsychiatric problems that might accompany this disorder) in patients with PD were identified.

However, it is acknowledged that tests suggested here are preliminary only, and is intended to further evaluate these measures in terms of their sensitivity (i.e. further evaluation with new groups of PD patients) and specificity (i.e. evaluating the final test selection with other patient groups such as Huntington's disease,

Alzheimer's dementia etc), and also with other confirmatory methods e.g., fMRI/MRI, EEG and eye-movements.

In addition, it is intended that the patients and their healthy controls will be followed up longitudinally. This longitudinal follow-up will serve to identify/confirm the characteristics of the patients who will go on to develop dementia. In this regard, it is expected that a greater percentage patients in the PD-MCI group will develop dementia than in the other two groups.

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Appendices

I - Ethnicity Questionnaire

Ethnicity of participant (Today's Date:)

Name:

Which ethnic group do you belong to?
Mark the space or spaces which apply to you.

ˆ New Zealand European

ˆ Mäori (iwi:)

ˆ Samoan

ˆ Cook Island Mäori

ˆ Tongan

ˆ Niuean

ˆ Chinese

ˆ Indian

ˆ OTHER Please state:

II - Health Check-List And Background Information

Health checklist and background for Healthy controls____M / F

Today's Date:

Full Name:	PD match:
Date of birth:	GP:
Satisfactory / corrected vision: Yes / No and hearing: Yes / No	

Current medications, including dose:

Other Comments:

Tick (and then underline) if any of the following exclusions (History or Current):

- ○ Aged <49 and > 80 yrs
- ○ Involved in any current therapeutic trial
- ○ Moderate or severe head injury / stroke / other neurological impairment (specify:)
- ○ Neurosurgery
- ○ Major medical illness (cardiovascular; diabetes req insulin; severe migraine; other:)
- ○ Significant psychiatric illness requiring hospitalization (specify:)
- ○ Major depression in last 6 months
- ○ Dementia / hallucinations
- ○ Indication of excess alcohol or substance abuse
- ○ Medications known to have a significant effect on CNS other than anti-PD medication
- ○ Diagnosis or special education for a learning disability

Enter ID #_____check below only after initial tests

- ○ Mini-Mental Status score <24
- ○ Pre-morbid IQ estimate < 85

Continued…

Full Name:	PD match:
Date of birth:	
GP:	

Contact tel. Number (s):_____

1) What language do you and your family speak at home or at work?_____

2) Years of education (in years post age 10/11, that is <u>not</u> counting primary school)?_____

3) Qualifications (indicate):

□ School qualification (For example: school certificate passes, sixth form qualification, higher school qualification, University Bursary Entrance Exam).

□ Vocational qualification (For example: trade certificate, technicians certificate, apprenticeships, national certificate, national diploma, advanced trade certificate bringing certificate, pre vocational certificate).

□ Higher qualification (For example: undergraduate diploma or certificate, New Zealand diploma or certificate, BA, BSc, MA, Ph.D., post-graduate diploma).

□ None of the above

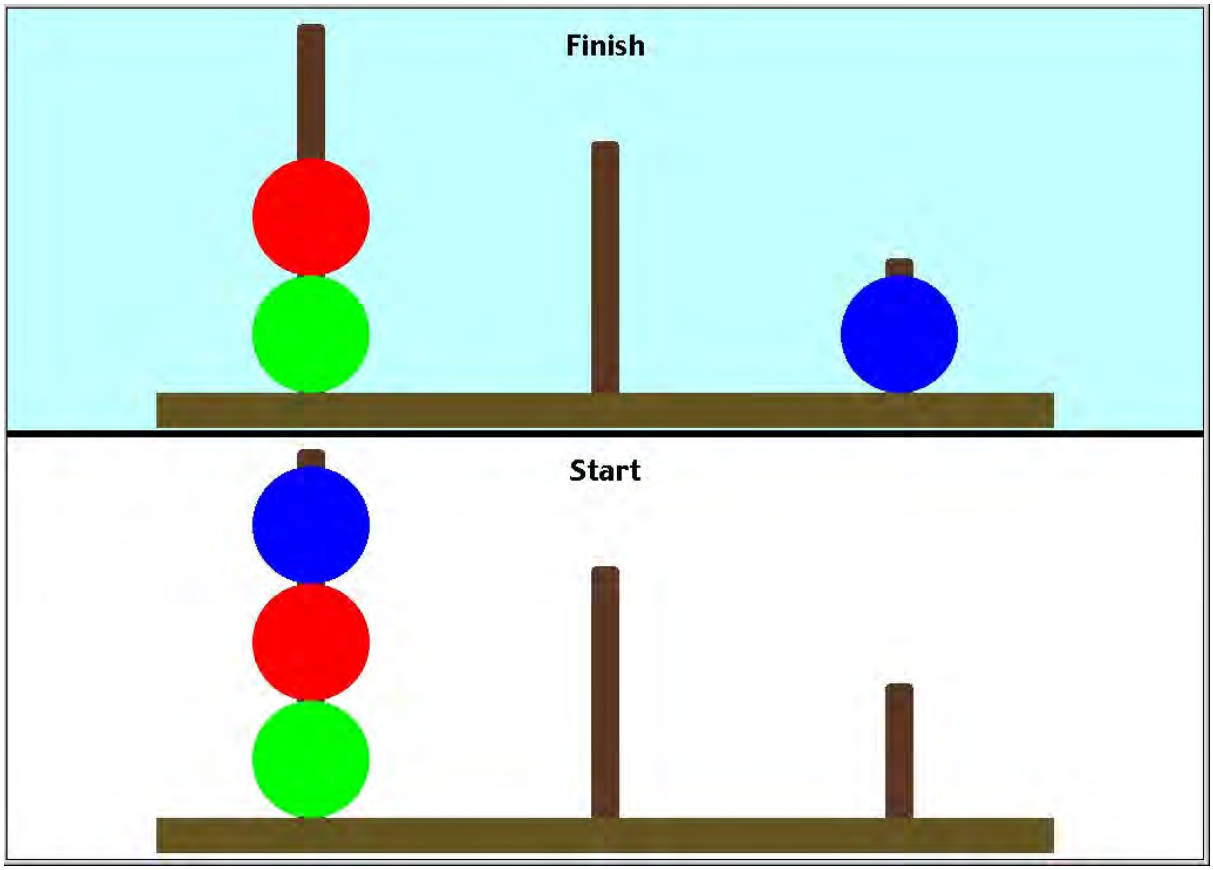
4) Which day(s) and time you are most likely to be free to take part in the study?_____

5) Caffeine drinks (coffee, tea, chocolate, caffeinated soft drinks)
<u>Per day</u>: None / Little (One cup or can per day)
Moderate (2 or 3)
Heavy (4 or more)

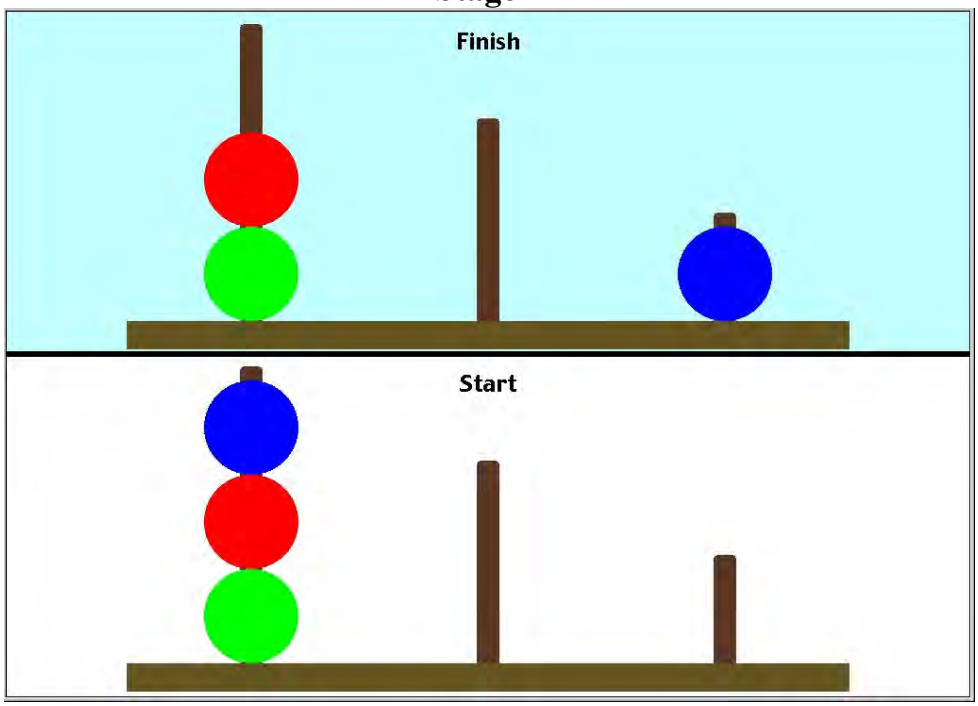
6) Alcohol <u>Daily average (ALAC guide:</u>
<u>Per day:</u> None / Little (less than moderate daily average)
Moderate (1/3 to 1 spirit;1-2.5 glass wine; or 2-5 glasses of beer; as a daily average)
Heavy (more than moderate daily average)

III - Instructions For The Tower Of London – Revised

Tower of London Task



Stage 1



The participant will be shown a display with two sets of three coloured balls, one on the top half of the screen and one on the bottom half of the screen.

The TOL Task Overview

The participant must make the bottom half of the screen (marked start) look like the top half of the screen (marked with the word finish and is coloured blue to remind the participant what they are aiming for)

The balls can be moved one at a time by touching the ball and then touching the position it is to be moved to.

NOTE: When the touch screen is activated, the time from the appearance of a new arrangement on the screen until the first ball is touched is taken as the planning time. So it is very important to emphasise that the individual carefully plan their moves before they touch the first ball.

All information for the examiner is inside the brackets<> Bolded words in the boxes are to be read out by the examiner.

< IF AT ANY TIME THE PARTICIPANT APPEARS DISTRESSED OR UNABLE TO CONTINUE, ESCAPE BY PRESSING THE apple and T KEY TOGETHER>

Instructions:

<1. Double click on tower of London icon which is on the desktop>
<2. Go to file and open "new subject file. Enter subject details>
<3. Go to Tower and open trial file>
<4. Open TOL-Part 1>
<5. Go to Tower and click on show trial file>

< A grey screen will appear first. After instructions have been given press the space bar to reveal the problem. After the participant has completed the problem press the space bar to display the grey screen and give the new instructions. This sequence is repeated for all problems>

Introduction

The next Task is a planning task.

You might recall a similar task from last time.

We have designed a NZ version which should work better than those designed overseas.

Problems 1 and 2 (Grey screen will be visible)

<Press the space bar to reveal the first TOL.
For the first stage of testing the minimum number of moves required to solve the problem will appear in the right hand side of the screen.>

For this task you will be shown a number of planning problems.

On the screen there are two arrangements of coloured balls, one on the top half of the screen and one on the bottom.

<point to the balls in the two arrangements>

The tall peg holds up to three balls, but no more than three balls.

The middle peg holds up to two balls.

The short peg holds only one ball. <use model to demonstrate this>

You are to plan how to make the colour and position of the balls in the

bottom half of the screen (the start < point>**) look exactly like the top half (the finish** < point>**).**

The background of the top half is coloured blue to remind you which pattern you are copying. That is, plan how you would change the start area here <point> **to end up looking exactly like the finish area** <point>. **<**point to the two halves of the screen>

***Before* you touch the screen** <pause> **remember to plan your moves first. The most important thing is to solve each problem in the <u>minimum</u>** <pause> **number of moves.**

When you have finished planning, then you can move the balls. To move a ball all you have to do is touch the ball and then touch the position that you want the ball to move to.

When you touch a ball you will hear a sound and the ball will flash. If you change your mind about the ball you want to move just touch the ball again.

On the side of the screen is a number < point> **This tells you the minimum moves that it takes to make the bottom pattern look exactly like the top.**

<Demonstrate the activating and deactivating of the balls
<u>then move ball to goal state</u>>

<There are a limited number of moves that the participant will be able to make before the problem will be discontinued (double the minimum + 1) in which case the screen will display the statement "Task end">

Now the arrangement of the balls in the bottom half of the screen looks exactly like the top half.

There are some simple rules to remember when you are planning your moves:

1. **You can only move one ball at a time** <pause>
2. **You can only move the top ball on any peg** <pause>
3. **You cannot place two balls in the same position** <pause>
4. **You can move to an adjacent peg** <pause; point>
5. **You can jump over the middle peg** <pause; point>

< Demonstrate rules on the model>

We will start with some 1 and 2 move problems so you can get used to the task, then we will move on to some three move problems

<press space bar and grey screen will appear with the words

"Please Remember
To Plan ALL Your Moves Carefully
Before Touching Any Ball"

<IMPORTANT: Remember to emphasis that they must plan which moves they are going to make before they touch the screen>

The next problem requires one move. Plan carefully how to make the bottom half look exactly the same as the top half, before you touch any
of the balls.

When you are ready, touch the ball you want to move and then touch the position you would like to move it to.

< when they complete the problem or they run out of moves, press the space bar and a grey
screen will appear.>

< To display the next problem the examiner must press the space bar>

< If the participant seems confused or unsure the following prompts may be used:>

Touch the ball you want to move

Touch the position you would like to move the ball to

You can jump over the middle peg

If you change your mind touch the ball again and it will stop flashing

Remember if you touch the ball twice you will not be able to move it

<they will have activated and deactivated the ball without moving it>

<If a participant seems to be impulsive prompt with>

Remember to *plan* your moves carefully, before you touch any of the balls.

Problems 3 and 4

(grey screen should be visible at the start of each problem)

<Problems 3 and 4 are two move problems. While the grey screen is visible introduce each by saying>

This is a two move problem.
Remember to plan your moves first.
The most important thing is to plan how to solve the problem in the minimum moves.
Think carefully about ALL the moves that are required to make the bottom pattern look exactly like the top pattern.
Don't start moving any ball until you are certain you know which moves
you are going to make.
When you are certain you know all the moves you will have to make then start moving the balls.

< press the space bar to reveal the problem>

Movement Time (Important)

< at the end of Phase 1 participants will be presented with a series of three towers that do not require any moves. For these towers participants will only be required to touch the ball they are instructed to touch>

< Prepare the model with a red ball in the left hand peg, a blue ball on the middle peg and a green ball on the right had peg. For the first tower instruct the participant with>

Now we are going to do something different.

When the next tower appears I would like you to touch the red ball as quickly as you can. The red ball will be in this position <point to the model>

<for the second tower instruct the participant with>

For the next problem I would like you to touch the Blue ball as quickly
as you can. The blue ball will be in this position <point to the model>

<for the Third tower instruct the participant with**>**

For the next problem I would like you to touch the green ball as quickly
as you can. The green ball will be in this position <point to the model>

Phase 2

1. <Go to Tower and open trial file>
2. <Open TOL-Part 2>
3. <Go to Tower and click on show trial file>

Problems 5-16

<grey screen should be visible at the start of each problem.
There are 12 three move problems>

IMPORTANT: A participant will not continue to the next stage if they do not get 9/12 problems solved correctly within "double the minimum +1". The examiner must count the number of problems correctly solved.

< For the first two three move problems (problems 5 and 6) read the following instructions>

These next problems are all three move problems.
Remember to plan your moves first.
The most important thing is to plan how to solve the problem in the minimum moves.
Think carefully about ALL the moves that are required to make the bottom pattern look exactly like the top pattern
Don't start moving any ball until you are certain you know which moves
you are going to make.
When you are certain you know all the moves you will have to make then start moving the balls.

< for subsequent problems read the following>

Remember to plan your moves first.
The most important thing is to plan to solve the problem in the minimum
moves.

< If necessary prompt with the following>

Think carefully about ALL the moves that are required to make the bottom pattern look exactly like the top pattern.

Tower of London Phase 3

. <Go to Tower and open trial file>
2. <Open TOL-Part 3>
3. <Go to Tower and click on show trial file>

<There are 9 problems in this part of the task in the order of
(3,4,5,3,4,5,3,4,5)

< Bring up second TOL trial file. A grey screen will be visible at this stage introduce the first problem by saying>

For this next stage the problems will get a bit harder but the rules will
be the same.
Remember to first plan all of the moves required to solve the problem.
The most important thing is to plan to solve the problem in the minimum moves.
Think carefully about ALL the moves that are required to make the bottom pattern look exactly like the top pattern
Don't start moving any ball until you are certain you know which moves you are going to make
When you are certain you know all the moves you will have to make then start moving the balls.
This is a 3 Move problem

<press space bar to show first problem>

< introduce problems 2-8 by saying one of the following statements order>

Remember to plan your moves first. The most important thing is to plan to solve the problem in the minimum moves.
This is a …. move problem.

<If necessary use the following prompt>

Think carefully about ALL the moves that are required to make the bottom pattern look exactly like the top pattern

Movement Time (Important)

< at the end of Phase 3 participants will be presented with a series of three towers that do not require any moves. For these towers participants will only be required to touch the ball they are instructed to touch>

< Prepare the model with a green ball in the left hand peg, a red ball on the middle peg and a blue ball on the right had peg. For the first tower instruct the participant with>

Now we are going to do something different.

When the next tower appears I would like you to touch the green ball as
quickly as you can. The green ball will be in this position <point to the model>

<for the second tower instruct the participant with>

For the next problem I would like you to touch the red ball as quickly as you can. The red ball will be in this position <point to the model>

<for the Third tower instruct the participant with>

For the next problem I would like you to touch the blue ball as quickly as you can. The blue ball will be in this position <point to the model>

IV - Gambling Task Instructions

Decision Making Task Instructions

(read these out loud to participant)

- In front of you on the screen, there are 4 decks of cards A,B,C,D.
- I want you to select one card at a time, by clicking on the card, from any deck you choose.
- Each time you select a card, the computer will tell you that you have won some money. I don't know how much money you will win. You will find out as we go along. Every time you win, the green bar gets bigger.
- Every so often, however, when you click on a card, the computer tells you that you won some money, but then it says that you lost some money too. I don't know when you will lose, or how much you will lose. You will find out as we go along. Every time you lose, the green bar gets smaller.
- You are absolutely free to switch from one deck to the other at any time, and as often as you wish.
- The goal of the game is to win as much money as possible and if you cant' win, avoid losing money as much as possible.
- You won't know when the game will end. You must keep playing until the computer stops.
- I am going to give you this $2000 credit, The green bar, to start the game. The red bar here is a reminder of how much money you borrowed to play the game, and how much money you have to pay back before we see how much you won or lost.
- It is important to know that just like in a real card game, the computer does not change the order of the cards after the game starts. You may not be able to figure out exactly when you will lose money, but the day is fair. The computer does not make you lose at random, or make you lose money based on the last card you picked. Also, each deck contains an equal number of cards of each colour, so the colour of the cards does not tell you which decks are better in this game. So you must not try to figure out what the computer is doing. All I can say is that some decks are worse than others. You may find all of them bad, but some are worse than others. No matter how much you find yourself losing, you can still win if you stay away from the worst decks. Please treat the play money in this game as real money, and any decision on what to do with it should be made as if you were using your own money.

Permission to use this task was kindly provided by Antoine Bechara, Department of Neurology, Iowa.

V - Continuous Performance Task Instructions

Continuous Performance Task Instructions

Read out the following:

" The computer is going to display letters of the alphabet on the screen. Your task is to press the space bar here whenever a letter appears on the screen. However, there is an exception to this - don't press the space bar if an X is displayed. Please respond as fast as you can, but also as accurately. Accuracy is more important than speed."

VI - Words Used For Daneman And Carpenter Reading Span Task - Study One

Reading Span Score Sheet

Subject: _____
Reading Span: _____
Total correct: _____

PRACTICE:

1) Work
Earth

2) Ground
Friend

3) Time
Asleep

4) Purple
Mouth

5) Parade
Dog

SET 2:

Wet	Hand	*Man*
House	*Car*	Town

SET 3:

Crocodile	*Pounding*	Watch
Village	*Fire*	*Eraser*
Trouble	Forever	Century

SET 4:

Down	*Point*	*History*
Answer	*Cage*	Still
Carpet	Concern	*Tide*
Snow	*Dance*	Base

SET 5:

Air	*Next*	*Plane*
Water	*Fence*	Pale
Lighting	Breath	Hard
Forward	Burst	*Line*
Garage	*Jury*	Song

SET 6:

Don't	Smile	Resort
Glance	Open	One
Sunburn	*Contact*	*Croak*
Nest	Trap	*Attack*
Apartment	Mist	*Horizon*
War	*Outside*	*Feather*

VII - Words Used For Daneman And Carpenter Reading Span Task - Study Two

Daneman & Carpenter

Participant ID: _____

Date: _____

	Makes sense (Y/N)	Score 0 or 1	Recalled (check)
Practice			
Work	Y / ***N***		
Earth	Y / ***N***		
Ground	Y / ***N***		
Friend	***Y*** / N		
Time	Y / ***N***		
Asleep	***Y*** / N		
Purple	***Y*** / N		
Mouth	Y / ***N***		
Parade	***Y*** / N		
Dog	Y / ***N***		
Set 2			
Wet	***Y*** / N		
House	***Y*** / N		
Hand	***Y*** / N		
Car	Y / ***N***		
Man	Y / ***N***		
Town	***Y*** / N		
Set 3			
Crocodile	Y / ***N***		
Village	Y / ***N***		
Trouble	***Y*** / N		
Pounding	Y / ***N***		
Fire	Y / ***N***		
Forever	***Y*** / N		
Watch	***Y*** / N		
Eraser	Y / ***N***		
Century	***Y*** / N		

	Makes sense (Y/N)	Score 0 or 1	Recalled (check)
Set 4			
Down	***Y*** / N		
Answer	Y / ***N***		
Carpet	***Y*** / N		
Snow	Y / ***N***		
Point	Y / ***N***		
Cage	Y / ***N***		
Concern	***Y*** / N		
Dance	Y / ***N***		
History	Y / ***N***		
Still	***Y*** / N		
Tide	Y / ***N***		
Base	***Y*** / N		
Set 5			
Air	***Y*** / N		
Water	Y / ***N***		
Lightning	Y / ***N***		
Forward	***Y*** / N		
Garage	***Y*** / N		
Next	Y / ***N***		
Fence	Y / ***N***		
Breath	***Y*** / N		
Burst	***Y*** / N		
Jury	Y / ***N***		
Plane	Y / ***N***		
Pale	***Y*** / N		
Hard	***Y*** / N		
Line	Y / ***N***		
Song	***Y*** / N		

Total Y/N identified correctly ☐

Total Recalled ☐

Reading Span (circle one)

2 2.5 3 3.5 4 4.5 5

VIII - Word Sequencing Test Instructions And Words Used In Study One

WORD SEQUENCING TEST

Instructions and Word List Study One.

1. Select 15 cards
2. Instruct the participant to read each word aloud and to try to remember the order in which the words appeared.

Say " *I want you to read each card out loud as I show them to you and I also want you to try to remember the order in which the words appeared".*

3. Present one card in a random order at the rate of one 3 seconds per word
4. Following the word presentation, arrange the duplicate set of words on the table in front of the participant in a random two-dimensional array.
5. Instruct the participant to place the words on the table in the same sequence in which they were originally presented by the examiner from the first word to the last word

Say *" Now can you please place the words on the table in the same order in which they were originally shown to you from the 1st word to the last. If you are not sure give it your best guess"*

6. Allow as much time as needed.

Word List

1. Air
2. Free
3. Name
4. Show
5. Kind
6. Keep
7. Full
8. Word
9. Whole
10. Job
11. Turn
12. Act
13. Door
14. Run
15. True.

IX - Word Sequencing Test Instructions And Words Used In Study Two

WORD SEQUENCING TEST
Instructions and Word List Study Two.

Select 8 cards

Instruct the participant to read each word aloud and to try to remember the order in which the words appeared.

Say " *I want you to read each card out loud as I show them to you and I also want you to try to remember the order in which the words appeared".*

Present one card in a random order at the rate of one 3 seconds per word

Following the word presentation, arrange the duplicate set of words on the table in front of the participant in a random two-dimensional array.

Instruct the participant to place the words on the table in the same sequence in which they were originally presented by the examiner from the first word to the last word

Say *" Now can you please place the words on the table in the same order in which they were originally shown to you from the 1st word to the last. If you are not sure give it your best guess"*

Allow as much time as needed.

Word List

1. Door
2. Show
3. True
4. Name
5. Turn
6. Job
7. Free
8. Kind

X - The Fatigue Severity Scale

FATIGUE SEVERITY SCALE

Below is a list of common symptoms of **physical** fatigue. Please read each item carefully and indicate how much you agree or disagree with each statement.

1 indicates strongly disagree and 7 indicates strongly agree.

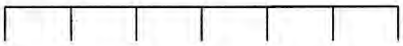
1. My motivation is lower when I am fatigued.

1 2 3 4 5 6 7

2. Exercise brings on my fatigue.

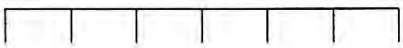
1 2 3 4 5 6 7

3. I am easily fatigued.



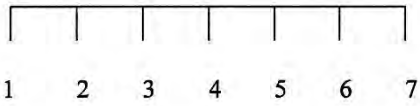
1 2 3 4 5 6 7

4. Fatigue interferes with my physical functioning.

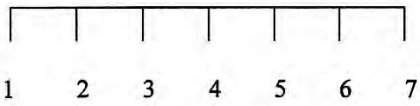


1 2 3 4 5 6 7

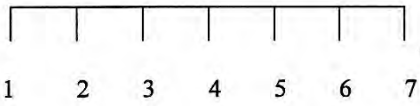
5. Fatigue caused frequent problems for me.



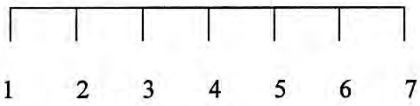
6. My fatigue prevents sustained physical functioning.



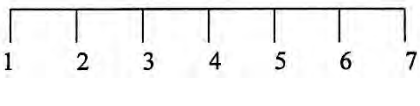
7. Fatigue interferes with carrying out certain duties and responsibilities.



8. Fatigue is among my three most disabling symptoms.



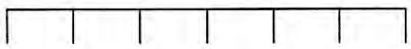
9. Fatigue interferes with my work, family, or social life.



Below is a list of common symptoms of **mental** fatigue. Please read each item carefully and indicate how much you agree or disagree with each statement.

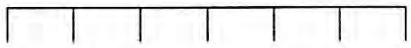
1 indicates strongly disagree and 7 indicates strongly agree.

1. My motivation is lower when I am fatigued.



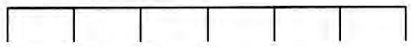
1 2 3 4 5 6 7

2. Exercise brings on my fatigue.



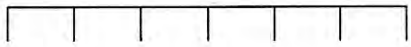
1 2 3 4 5 6 7

3. I am easily fatigued.



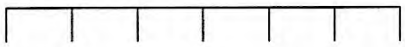
1 2 3 4 5 6 7

4. Fatigue interferes with my physical functioning.



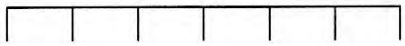
1 2 3 4 5 6 7

5. Fatigue caused frequent problems for me.



1 2 3 4 5 6 7

6. My fatigue prevents sustained physical functioning.

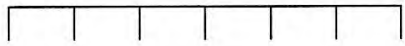


1 2 3 4 5 6 7

7. Fatigue interferes with carrying out certain duties and responsibilities.

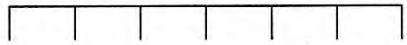
1 2 3 4 5 6 7

8. Fatigue is among my three most disabling symptoms.



1 2 3 4 5 6 7

9. Fatigue interferes with my work, family, or social life.



1 2 3 4 5 6 7

XI - Daily Sleep And Symptom Diary

<u>Daily record to monitor your Parkinson's disease symptoms</u>
We would like you to record your Parkinson's symptoms for 24 hours
Prior to your next visit.

Please use the hour slots on the facing page to help you keep track of your symptoms.

Just fill in any details as and when you can.

Try not to leave it too long in case you forget, but do not worry if you do not remember.

Indicate the Following if you can:

1. **Note the time on each occasion you take/took your Parkinson's medication(s).**
2. **For each hourly interval record whether you were "on, off or asleep"**

ON- Means when you were free of many or most of your Parkinson's symptoms (when the drugs seem to provide reasonable relief). For this, just write "On," for that time or block of time.

OFF- Means when you have many or most Parkinson's symptoms from which you are normally free if the anti-Parkinson drugs are working. For this, just write "Off" and give a rough estimate of how long (that is, the duration before any benefits come back).

ASLEEP: for the hours you are asleep, enter asleep in this block of time

	Diary Hours Date: Day:
6.00am	
7.00	
8.00	
9.00	
10.00	
11.00	
12.00	
1.00	
2.00	
3.00	
4.00	
5.00	
6.00	
7.00	
8.00	
9.00	
10.00	

XII - Letter From The Neurologists Inviting Participation In The Study

Date

Name
Address

Dear…….,

We are doing some NEW research on language, memory and attention in people in Christchurch who have been diagnosed with Parkinson's disease. We would very much like your help if you can. Please look at the enclosed information sheet. If you are willing to have Audrey McKinlay contact you about this research, please either call her or place the reply slip in the pre-paid addressed envelope and then post that back to us.

Thank you for your time.

Professor Tim Anderson MD, FRACP
Neurologist

Dr John Fink FRACP
Neurologist

XIII - Information Sheet For Parkinson's Disease Patients For Study One

Project Title: Thinking and language skills in people with Parkinson's disease

Name:

Address: Date:

We would like to invite you to take part in a new research study, which is funded by the Canterbury Medical Research Foundation. This study is being conducted by neurologists, Dr. Tim Anderson and Dr. John Fink, and psychologists Dr. Paul Barrett, Dr John Dalrymple-Alford and Audrey McKinlay. This study will provide information on thinking (including attention and memory) and language in people with Parkinson's Disease in the Canterbury region. These responses will be compared with those obtained from people who do not have any neurological condition.

This information sheet has either been given or forwarded to you by your neurologist or sent to you by your local Parkinson's society. If you are interested in taking part in the study, please contact Audrey McKinlay (366 7001 Ext. 7885) or Dr. John Dalrymple-Alford ("John D-A" 364 2998 or 366 7002 Ext. 6382) who will be pleased to answer any questions you may have at this time.

If you agree to participate in this research, please note that you are free to withdraw at any stage. If you choose to withdraw, you do not need to

give a reason and this will not affect your future care or treatment. You will continue your regular medication during the course of this study.

The various tests follow standard procedures. Past research has often missed detail that would improve the conclusions that can be made. We therefore ask you to attend on up to three separate visits. This is necessary to minimise the length of each visit and allow for adequate breaks during each visit. Most tests or subtests require a short period of concentration (5-10 minutes). The first visit is at the Neurology Department at Christchurch Hospital. The next two are in the Psychology Department at the University of Canterbury. These three visits are as follows:

Visit 1. (about 2-3hrs, including breaks)
This visit will gather some general information on your medical status, including the current condition of your Parkinson's disease, and your general cognitive functioning (a short summary of your overall ability). This visit will help us to confirm whether you meet the scientific criteria for this study. You will also be asked to take home some standard self-report questionnaires to fill in and return (up to an hour; either by pre-paid post or at to the next visit). We may then invite you to return for the next two visits.

Visit 2. (about 2-3 hours, including breaks)
This visit will provide more specific information on memory, language and planning skills. You will also be asked to take home some new self-report questionnaires to fill in and return at the next visit. If you consent, we will also include a questionnaire for your spouse or caregiver to complete.

Visit 3. (about 2-3 hours, including breaks)
This final visit will include tests of language skills and other every day activities.

Reimbursement
All participants will be reimbursed $15 for each visit towards transport costs (or the cost of a taxi, if required, in the Christchurch region).

Confidentiality
Please note that all information provided for this study will be treated in the utmost confidence. All personal information will be securely stored, accessible only by the principal investigators of this study. Your identity will not be disclosed in any reports based on information from this study. We will on your consent notify your neurologist of your participation in this study, but will not disclose any information on your language and thinking skills unless requested in writing by you.

Information regarding the findings of this study
Although individual results will be kept strictly confidential, a summary of the findings from this research will be made available to all of the participants and we will be pleased to send you a copy on completion of the study. The overall results gathered will be used for the purposes of this study and will contribute to the scientific knowledge on Parkinson's disease. They will also form part of a doctoral thesis by Audrey McKinlay. The information obtained may be added to that obtained in future studies, because it is necessary to have large data-sets to improve our accuracy in describing the overall effects of Parkinson's disease.

Support Person
You are invited to bring a partner/friend /family member or support person with you to any visit. An adjacent room will be available for them to wait if you desire.

Significant Other
If you consent, we would also like you to nominate a person who knows you well and could provide some information about your general demeanour and every day routines. If this person is also your support person, information could be collected when you attend one of the sessions. Otherwise, if you prefer, one of the researchers could visit them in their home.

Participation
Your participation in the study is entirely voluntary. You do not have to answer all the questions in the study and you are free to withdraw at any time for any reason.

If you have any questions or concerns about any aspect of this study you are welcome to contact either Audrey McKinlay (366 7001 Ext. 7885) or Dr. John Dalrymple-Alford ("John D-A" 364 2998 or 366 7002 Ext. 6382).

If you have any queries of concerns about your rights as a participant in this study you may wish to contact a Health and Disability Advocate (03) 377 7501 or 0800 377 766 (outside of Christchurch).

In the unlikely event of a physical injury as a result of your participation in this study, you will be covered by accident compensation legislation within its limitations. If you have any questions about ACC please feel free to ask the researcher for more information before you take part in this study.

This study has received ethical approval from the Canterbury Ethics Committee and we are committed to treating all of the study participants in a fair and ethical manner.

We would greatly value your help. Thank you for considering this request.

<u>If you are interested in taking part in the study, please confirm with either of us below.</u>

Audrey McKinlay (366 7001 Ext 7885)

PhD Candidate
Department of Psychology
University of Canterbury

John Dalrymple-Alford ("John D-A" 364 2998 or 366 7002 Ext. 6382).

Senior Lecturer
Department of Psychology
University of Canterbury

XIV - Reply Slip For Study One

THINKING AND LANUGUAGE SKILLS IN PEOPLE WITH PAKINSON'S DISEASE

REPLY SLIP

I have read the information sheet and would be willing to be contacted regarding participation in the project "Thinking and language skills in people with Parkinson's disease."

CONTACT DETAILS:

Name: _____

Telephone number : _____

Most convenient contact time: _____

XV - Ethics Approval For Study One

Canterbury
Ethics Committees
4th Floor, 250 Oxford Terrace
P.O. Box 3877
Christchurch
Fax (03) 372 1015

15 June 2004

Christchurch Brain Research Group
Department of Psychology
University of Canterbury
Private Bag 4800
Christchurch

Complex language, mediating factors and Parkinson's disease
Investigators: Dr J Dalrymple-Alford, A/P T Anderson, Dr J Fink, Dr P Barrett, A McKinlay, G Averill-Roper
Ethics reference: CTY/03/04/068
Information sheet for participants with Parkinson's Disease version dated 12-6-2003
Information sheet for controls version dated 12-6-2003
Consent form v2 June 03
Consent to obtain additional information from significant other v 2 June 03

Thank you for the progress report for the above study. Ethical approval is confirmed until 31 July 2005.

The Committee looks forward to your final report at that time.

Yours sincerely,

Sally Cook
Committee R Administrator
Email: sally_cook@moh.govt.nz
Phone: (03) 372 3018

XVI - Advertisement For Healthy Controls

Research Volunteers Wanted
This project has been approved by the Canterbury Ethics Committee

Healthy older people between the ages of 50-80 years are wanted as control participants for a study that examines thinking and language in people with Parkinson's Disease. Evaluations of memory, attention, and language abilities will be assessed over three visits of 2-3 hours each. Participants will be reimbursed with a $20.00 petrol vouchers for each visit.

If you are interested in taking part in this study please contact Audrey McKinlay (Clinical Psychologist) 3667001(Ext 7885).

XVII - Information Sheet For Healthy Controls

Information Sheet: For potential participants who are "Healthy Controls" in that they have not been diagnosed with any neurological disorder

Project Title: Thinking and language skills in people with Parkinson's disease

Name:

Address: Date:

This information sheet is to summarise the nature of our study and follows our recent telephone contact through the Canterbury University Psychology Department's list of research participants.

We would like to invite you to take part in a new research study on the effects of Parkinson's disease. This study is being conducted by neurologists, Dr. Tim Anderson and Dr. John Fink, and psychologists Dr. Paul Barrett, Dr John Dalrymple-Alford and Audrey McKinlay. This study is funded by the Canterbury Medical Research Foundation.

Parkinson's disease is a neurological condition that affects about 100 or so people in every 100,000, but is more common in older people. This condition affects movement, but it may also affect thought (including

attention and memory) and language. The study will provide information on thinking and language in people with Parkinson's Disease in the Canterbury region. To understand these effects, we need to compare the abilities of Parkinson's disease patients with that of "healthy controls" who do not have any neurological disorder. This is why we are contacting you to ask for your help in this important work. If you agree to participate in this research, please note that you are free to withdraw at any stage. If you choose to withdraw, you do not need to give a reason and this will not affect you in any way in the future.

Audrey McKinlay {or named research assistant} will telephone you to see if you are interested in taking part in this study. She will be pleased to answer any questions you may have at this time. Please feel free to take up to a month to decide if you would like to help. Potential participants will be contacted from April 2003 through to April 2005.

The various tests follow standard procedures. Past research has often missed detail that would improve the conclusions that can be made. We therefore ask you to attend on up to three separate visits. This is necessary to minimise the length of each visit and allow for adequate breaks during each visit. Most tests or subtests require a short period of concentration (5-10 minutes). The first visit is at the Neurology Department at Christchurch Hospital. The next two are in the Psychology Department at the University of Canterbury. These three visits are as follows:

Visit 1 (about 2-3 hrs, including breaks)**.**
This visit will gather some general information on your medical status and your general cognitive functioning (a short summary of your overall ability). This visit will help us to confirm whether you meet the scientific criteria for this study. You will also be asked to take home some standard self-report questionnaires to fill in and return (either by pre-paid post or at to the next visit). We may then invite you to return for the next two visits.

Visit 2. (about 2-3 hrs, including breaks).
This visit will provide more specific information on memory, language and planning skills. You will also be asked to take home some new self-report questionnaires to fill in and return at the next visit. If you consent, we will also include a questionnaire for your spouse or a close friend to complete.

Visit 3. **(**about 2-3 hrs, including breaks).

This final visit will include tests of language skills and other every day activities.

Reimbursement
All participants will be reimbursed $15 for each visit towards transport costs (or the cost of a taxi, if required, in the Christchurch region).

Confidentiality
Please note that all information provided for this study will be treated in the utmost confidence. All personal information will be securely stored, accessible only by the principal investigators of this study. Your identity will not be disclosed in any reports based on information from this study.

Information regarding the findings of this study
Although individual results will be kept strictly confidential, a summary of the findings from this research will be made available to all of the participants and we will be pleased to send you a copy on completion of the study. The overall results gathered will be used for the purposes of this study and will contribute to the scientific knowledge on Parkinson's disease. They will also form part of a doctoral thesis by Audrey McKinlay. This information will be added to that obtained in future studies, because larger data-sets will improve our accuracy on the overall effects of Parkinson's disease.

Support Person
You are invited to bring a partner/friend /family member or support person with you to any visit. An adjacent room will be available for them to wait if you desire.

Significant Other
If you consent, we would also like you to nominate a person who knows you well and could provide some information about your general demeanour and every day routines. If this person is also your support person, information could be collected when you attend one of the sessions. Otherwise, if you prefer, one of the researchers could visit them in their home.

Participation
Your participation in the study is entirely voluntary. You do not have to answer all the questions in the study and you are free to withdraw at any time for any reason.

If you have any questions or concerns about any aspect of this study you are welcome to contact either Audrey McKinlay (366 7001 Ext. 7885)

or Dr. John Dalrymple-Alford ("John D-A" 364 2998 or 366 7002 Ext. 6382).

If you have any queries of concerns about your rights as a participant in this study you may wish to contact a Health and Disability Advocate (03) 377 7501 or 0800 377 766 (outside of Christchurch).

In the unlikely event of a physical injury as a result of your participation in this study, you will be covered by accident compensation legislation within its limitations. If you have any questions about ACC please feel free to ask the researcher for more information before you take part in this study.

This study has received ethical approval from the Canterbury Ethics Committee and we are committed to treating all of the study participants in a fair and ethical manner.

We would greatly value your help. Thank you for considering this request.

<u>If you are interested in taking part in the study, please confirm with either of us below.</u>

Audrey McKinlay (366 7001 Ext 7885)

PhD Candidate
Department of Psychology
University of Canterbury

John Dalrymple-Alford ("John D-A" 364 2998 or 366 7002 Ext. 6382).

Senior Lecturer
Department of Psychology
University of Canterbury

XVIII - Consent Form For Participants In Study One

Departments of Psychology and Electrical & Computer Engineering and Speech & Language Therapy University of Canterbury

Departments of Neurology and Medical Physics & Bioengineering, Christchurch Hospital

Department of Medicine, Christchurch School of Medicine & Health Sciences University of Otago

Christchurch Brain Research Group

Consent Form

Project Title: Thinking and language skills in people with Parkinson's disease

I have been invited to take part in this study on thinking (including attention and memory) and language in people with Parkinson's disease. An information sheet has been provided on the aims and purpose of the study. I have read and understood the information it contained. I have been given an opportunity to discuss the study. I am satisfied with the answers that have been given. I have had time to consider whether to take part.

I understand that:

- Participation in the study is voluntary (my choice)
- I am free to withdraw from the study at any time and this will in no way affect my future healthcare.
- I am free to refuse to answer any questions that I do not want to answer.
- This study has approval from the Canterbury Ethics Committee.
- My participation in the study is confidential and no information that could identify me will be used in any reports that may be generated from this study.
- The compensation provisions for this study are covered by accident compensation legislation within its limitations.

I have been provided with information regarding who to contact if I have any concerns regarding the study.

(circle choice and cross out alternative below, as desired…)

(PD patients only) My neurologist can be informed of my participation YES NO/ NA

(All participants) I would like to receive a copy of the results of this study YES / NO

(All participants) My name will be added to / remain on a research register held in confidence by the Christchurch Brain Research Group on the understanding that I can choose to withdraw from this register at any time if I so choose YES / NO

I _____ (full name) hereby consent to take part in this study, entitled **"Thinking and language skills in people with Parkinson's disease"**.

Signature:_____ Date: _____

Researchers: John Dalrymple-Alford PhD, Tim Anderson MD, John Fink MD, Paul Barrett PhD, Audrey McKinlay MA, {RA name to be added}

Contact phone number: Audrey McKinlay (366 7001 Ext. 7885) or Dr. John Dalrymple-Alford ("John D-A" 364 2998 or 366 7002 Ext. 6382).

Project explained by:

_____

Project role:

_____

Signature: _____

Date:_____

XIX - Additional Statement For The Beck Depression Inventory

Please note that both the BDI (most commonly used in PD studies) and the GDS (generally regarded as more suitable for older patient groups) will be provided, in order to verify their suitability, similarity or otherwise in PD patients and controls for this study.

Additional Statement re the Beck Depression Inventory (the BDI)

Please note that the additional Statement re the BDI is *only* given to anyone who fits the following standard criteria. A score of 14 (or above) on the Beck Depression Inventory is used as a conservative threshold for detecting mild depression (14-19; moderate: 20-28; severe: 29-63). Symptoms indicative of depression are used simply for the purpose of specifying non-depressed individuals for the study (Note: a cut-off score of 17 is recommended by the BDI Manual for research purposes).

We feel that it is important to give some cautious feedback to the participant if they show a score above 13 on the BDI. Thus, ONLY in the event that one of the participants reveals a score of 14 or more on the BDI, the following statement will be given to the participant, for them to read, to fill in as they see fit, *and sign* (plus the researcher will give the participant a copy to retain).

Thinking and language skills in people with Parkinson's disease

Statement concerning the Beck Depression Inventory Score

As part of a study looking at thinking and language in people with Parkinson's disease, it was found that my Beck Depression Inventory Score (known as the BDI score) showed some indication of depressive symptoms.

This Inventory gave an estimate of a mild / moderate / severe (Researcher to circle as appropriate) level of depressive symptoms in my case.

I understand that this score is only indicative of depressive symptoms, but I have been advised by the Researcher that I should in the first instance contact my GP for further evaluation, should I choose.

I agree / disagree (Participant to circle their preference and cross out word which they find inappropriate) that the Researcher should contact me as a follow-up reminder,

and I agree / disagree (Participant to circle their preference and cross out word which they find inappropriate) that the Researcher may contact a friend, relative and/or GP or neurologist in confidence to provide me with further advice (Give name / contact here, if appropriate). I understand that this contact would be made concerning my BDI score, and not any other score or information provided during this study.

Name and phone of contact – provided by the participant:_____

I, _____ (print full name) fully understand the above statement, as amended by me, and understand that I will be given a signed copy of this statement.

Date_____

Signature of Participant_____

Signature of witness (normally, the researcher) _____

Name of witness_____

XX - Additional Statement For The Geriatric Depression Scale

Additional Statement re the Geriatric Depression Scale (GDS)

Please note that the additional Statement re the Geriatric Depression Scale is *only* given to anyone who fits the following standard criteria. A score of 9 (or above) on the Geriatric Depression Scale is used as a conservative threshold for detecting mild depression (scale indicates normal, 5 +/- 4; mildly depressed 15 +/- 6; very depressed, 23 +/- 5). Symptoms indicative of depression are used simply for the purpose of specifying non-depressed individuals for the study.

We feel that it is important to give some cautious feedback to the participant if they show a score above 9 on the GDS. Thus, ONLY in the event that one of the participants reveals a score of 9 or more on the GDS, the following statement will be given to the participant, for them to read, to fill in as they see fit, *and sign* (plus the researcher will give the participant a copy to retain).

Thinking and language skills in people with Parkinson's disease

Statement concerning the Geriatric Depression Inventory Scale (GDS)

As part of a study looking at thinking and language skills in people with Parkinson's disease, it was found that my score on the Geriatric Depression Inventory Scale (GDS) showed some indication of depressive symptoms.

This Inventory gave an estimate of a mild / moderate / severe (Researcher to circle as appropriate) level of depressive symptoms in my case.

I understand that this score is only indicative of depressive symptoms, but I have been advised by the Researcher that I should in the first instance contact my GP for further evaluation, should I choose.

I agree / disagree (Participant to circle their preference and cross out word which they find inappropriate) that the Researcher should contact me as a follow-up reminder,

and I agree / disagree (Participant to circle their preference and cross out word which they find inappropriate) that the Researcher may contact a friend, relative and/or GP or neurologist in confidence to provide me with further advice (Give name / contact here, if appropriate). I understand that this contact would be made concerning my GDS score, and not any other score or information provided during this study.

Name and phone of contact – provided by the participant:_____

I, _____ (print full name) fully understand the above statement, as amended by me, and understand that I will be given a signed copy of this statement.

Date_____

Signature of Participant_____

Signature of witness (normally, the researcher) _____

Name of witness_____

XXI - Consent To Obtain Information From Significant Other

Departments of Psychology and
Electrical & Computer Engineering
and Speech & Language Therapy
University of Canterbury

Departments of Neurology and
Medical Physics & Bioengineering,
Christchurch Hospital

Department of Medicine,
Christchurch School of
Medicine & Health Sciences
University of Otago

Christchurch Brain Research Group

Consent Form

Project Title: Thinking and language skills in people with Parkinson's disease

I have been invited to take part in this study on thinking (including attention and memory) and language in people with Parkinson's disease. An information sheet has been provided on the aims and purpose of the study. I have read and understood the information it contained. I have been given an opportunity to discuss the study. I am satisfied with the answers that have been given. I have had time to consider whether to take part.

I understand that:

- Participation in the study is voluntary (my choice)
- I am free to withdraw from the study at any time and this will in no way affect my future healthcare.
- I am free to refuse to answer any questions that I do not want to answer.
- This study has approval from the Canterbury Ethics Committee.
- My participation in the study is confidential and no information that could identify me will be used in any reports that may be generated from this study.
- The compensation provisions for this study are covered by accident compensation legislation within its limitations.

I have been provided with information regarding who to contact if I have any concerns regarding the study.

(circle choice and cross out alternative below, as desired…)

(PD patients only) My neurologist can be informed of my participation YES / NO/ NA

(All participants) I would like to receive a copy of the results of this study YES / NO

(All participants) My name will be added to / remain on a research register held in confidence by the Christchurch Brain Research Group on the understanding that I can choose to withdraw from this register at any time if I so choose

YES / NO

(continued)

I _____ (full name) hereby consent to take part in this study, entitled **"Thinking and language skills in people with Parkinson's disease"**.

Signature:_____ Date: _____

Researchers: John Dalrymple-Alford PhD, Tim Anderson MD, John Fink MD, Paul Barrett PhD, Audrey McKinlay MA, {RA name to be added}

Contact phone number: Audrey McKinlay (366 7001 Ext. 7885) or Dr. John Dalrymple-Alford ("John D-A" 364 2998 or 366 7002 Ext. 6382).

Project explained by:

_____

Project role:

_____

Signature: _____ Date:

_____

XXII- Over View Of The Initial Findings Sent Out To Participants In Study One

UNIVERSITY OF CANTERBURY
Te Whare Wānanga o Waitaha
CHRISTCHURCH NEW ZEALAND
Department of Psychology

VAN DER VEER INSTITUTE
for Parkinson's & Brain Research
www.vanderveer.org.nz

UNIVERSITY OF OTAGO
Department of Medicine

Research Project

Thinking and Language Skills in Parkinson's Disease

Progress report for participants and families

Overview of initial findings

November 2004

canterbury medical research foundation

This research was funded by the Canterbury Medical Research Foundation and the New Zealand Foundation for Research Science & Technology.

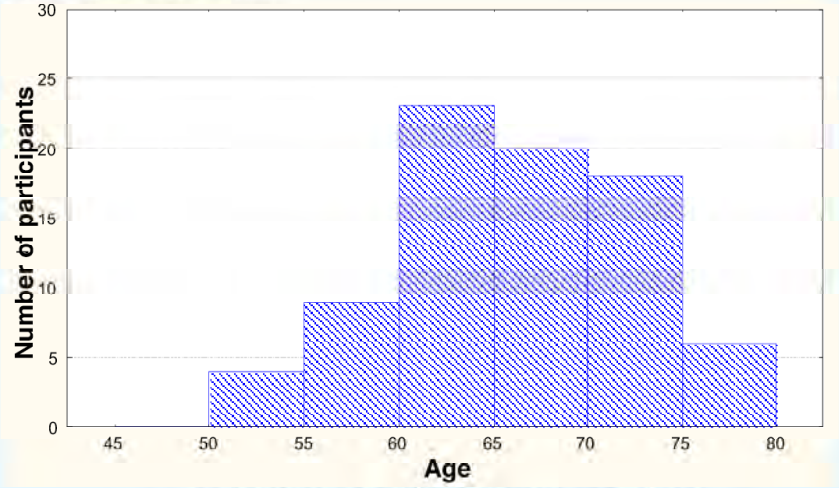
Foundation for RESEARCH SCIENCE & TECHNOLOGY

Thinking and Language Skills in Parkinson's Disease

We would like to thank all those who participated in the study, "Thinking and Language Skills in Parkinson's Disease". The initial phase of this study has been an overwhelming success. While the testing was extensive, almost all people were able to participate in the three testing sessions totalling over 9 hours, a marathon effort, for which we are most appreciative.

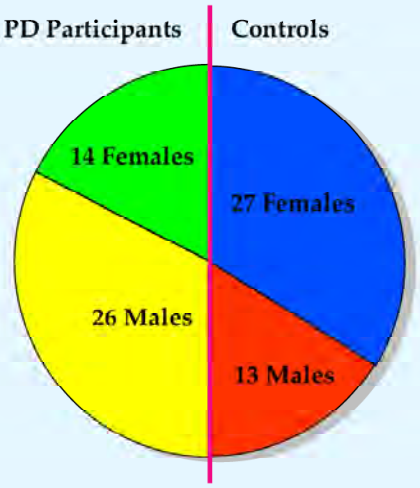
Participants

We have now analysed the data from 40 participants with Parkinson's disease (those who completed all 3 test sessions). These participants with Parkinson's disease were compared to 40 people without Parkinson's disease ("controls") who were matched interms of age and education.



Participants ranged from 52 to 77 years of age.

More men, than women with Parkinson's disease participated in the study. But there were more women than men volunteers without Parkinson's disease.



Background

The study was designed to identify some of the strengths and weaknesses in thinking, language and higher mental skills in individuals with Parkinson's disease. Past research findings in this area have, however, often been inconsistent and seldom addressed an adequate range of measures.

By starting with a wide range of measures we have been able to address several important questions. While there is still much to be done, we have uncovered some interesting new evidence on the variability of performance across patients.

Parkinson's Disease patients versus controls - mean for premorbid characteristic and current mental status.

	Controls		PD Patients	
	Mean	[Variability]	Mean	[Variability]
Education[1]	13.8	[2.6]	13.9	[2.6]
IQ[2]	110.2	[10.3]	109.1	[10.2]
DRS[3]	11.1	[2.4]	10.1	[2.6]

[1] Total years of education; [2] Estimated IQ;
[3] Rating scale of current mental status (adjusted for age and education).

The table above compares the Parkinson's disease patients and their age matched controls in terms of years of education, general intelligence and current mental status. The average of the two groups was equivalent on these three measures. Hence the outcomes described below can be more confidently related to the effects of Parkinson's disease, not pre-existing differences in general ability.

Outcomes

The assessments included test of general memory, mental agility (such as planning and problem solving), visual perception and complex language skills. When we compared individuals with Parkinson's disease with older adults without Parkinson's disease, we found that they were comparable on most measures of general memory. However, we have found new evidence of a cluster of deficits on mental agility, visual perception and complex language skills in many patients.

Findings from this research have been presented at the Eighth International Congress of Parkinson's Disease and Movement Disorders, which was held in Rome (June 2004), and The International College of Geriatric Psycho-neuropharmacology, in Switzerland (October 2004).

Future Directions

This study suggests some important new lines of research. One of these is that some traditional measures may be less sensitive than has been implied by previous research from Europe and the United Kingdom. We have also shown that, in future, researchers need to pay more attention to individual variability in performance in people who have Parkinson's disease.

Our initial findings have led to the development of new, much improved, tests that can now be followed up. We believe these new tests will be better suited for detecting cognitive deficits associated with Parkinson's disease. This research strategy is part of the process of developing a sensitive, yet short, sequence of tests. We hope that this shortened test sequence will become accepted as "best practice" by other researchers and health professional in the field of Parkinson's disease.

The most important advantage of these developments is that they may eventually lead to early identification of those individuals with Parkinson's disease who are experiencing cognitive problems. Progress along these lines will help future clinical management and guide appropriate treatment options.

One again we would like to thank you for taking part in this important research.

Tim Anderson, John Dalrymple Alford, Audrey McKinlay, John Fink

The next phase of our study is about to commence.

"Developing Cognitive Measures for Parkinson's Disease"

We would like to thank all those people who have agreed to participate in the follow up of the initial study.

We will be contacting you over the next few weeks.

We welcome any feedback or questions regarding the research in this newsletter. Please contact Audrey McKinlay (366 7001, Ext 7885) or John Dalrymple-Alford (366 7001, Ext 6998), Department of Psychology, University of Canterbury, Ilam Rd. Christchurch, Private Bag 4800.

XXIII - Information Sheet For Study Two

Van der Veer Institute
for Parkinson's and Brain Research
and Department of Psychology
University of Canterbury
Private Bag 4800
Christchurch
New Zealand

Information Sheet: For potential participants who are "Healthy Controls" in that they have not been diagnosed with any neurological disorder

Project Title: Developing cognitive measures for Parkinson's disease

As discussed by phone we would like to invite you to take part in our research study "Developing cognitive (thinking and reasoning) measures for Parkinson's disease". We will be pleased to answer any questions you may have. This research is an extension of our main study that focused on thinking and language skills in people with Parkinson's disease (PD). Based on our initial findings we now intend to develop new measures that may be more sensitive to the cognitive profile of PD patients. We are conducting this study in collaboration with neurologists, Dr. Tim Anderson and Dr. John Fink, and psychologist Dr. Paul Barrett. This study is funded by the Canterbury Medical Research Foundation.

To fully understand the effects of PD we need to compare the abilities of Parkinson's disease patients with that of "healthy controls" that do not have any neurological disorder. If you agree to continue to participate in this research, please note that you are free to withdraw at any stage. If you choose to withdraw, you do not need to give a reason and this will not affect you in any way in the future. Please feel free to take up to a month to decide if you would like to take part.

The various tests follow standard procedures. We ask you to attend on two separate visits. This is necessary to minimise the length of each visit and allow for adequate breaks during each visit. As before most tests or subtests require a short period of concentration (5-15 minutes) Visits will take place at the Psychology Department at the University of Canterbury. These two visits are as follows:

Visit 1. (About 2-2.5 hrs, including breaks)
This visit will gather some general information on your medical status, including your general cognitive functioning (a short summary of your overall ability). You will also be asked to take home some standard self-report questionnaires to fill in and return (up to 30 mins; either by pre-paid post or at to the next visit). If you consent, we will also include questionnaires for your spouse or caregiver to complete. Information from a spouse or caregiver is collected to provide an additional perspective, regarding your daily functioning, from a person who knows you well.

Visit 2. (About 2-3 hours, including breaks)
While the first visit will focus on medical status and more general aspects of cognitive functioning, this visit will provide more specific information on memory (both short and long term). Session 2 will also include measures of planning (ability to think ahead and organise) and decision making skills.

Reimbursement
All participants will be reimbursed $20 for each visit towards transport costs (or the cost of a taxi, if required, in the Christchurch region). We will reimburse petrol costs for participants who need to travel further distances.

Confidentiality
Please note that all information provided for this study will be treated in the utmost confidence. All personal information will be securely stored, accessible only by the principal investigators of this study. Your identity will not be disclosed in any reports based on information from this study.

Information regarding the findings of this study
Although individual results will be kept strictly confidential, a summary of the findings from this research will be made available to all of the participants and we will be pleased to send you a copy once the study

and data analyses have been completed. Results gathered will be used for the purposes of this study and will contribute to the scientific knowledge on Parkinson's disease. They will also form part of a doctoral thesis by Audrey McKinlay. This information will be added to that obtained in future studies, because larger data-sets will improve our accuracy on the overall effects of Parkinson's disease.

Support Person
You are invited to bring a partner/friend /family member or support person with you to any visit. A nearby room will be available for them to wait if you desire.

Participation
Your participation in the study is entirely voluntary. You do not have to answer all the questions in the study and you are free to withdraw at any time for any reason.

If you have any questions or concerns about any aspect of this study you are welcome to contact either Audrey McKinlay (366 7001 Ext. 7885) or Dr. John Dalrymple-Alford ("John D-A" 364 2998 or 366 7002 Ext. 6382).

If you have any queries of concerns about your rights as a participant in this study you may wish to contact a Health and Disability Advocate (03) 377 7501 or 0800 377 766 (outside of Christchurch).

In the unlikely event of a physical injury as a result of your participation in this study, you may be covered by ACC under the Injury Prevention, Rehabilitation and Compensation Act. ACC cover is not automatic and your case will need to be assessed by ACC according to the provisions of the 2001 Injury Prevention Rehabilitation and Compensation Act. If your claim is accepted by ACC, you still might not get any compensation. This depends on a number of factors such as whether you are an earner or non-earner. ACC usually provides only partial reimbursement of costs and expenses and there may be no lump sum compensation payable. There is no cover for mental injury unless it is a result of physical injury. If you have ACC cover, generally this will affect your right to sue the investigators. If you have any questions about ACC, contact your nearest ACC office or the investigator.

This study has received ethical approval from the Canterbury Ethics Committee and we are committed to treating all of the study participants in a fair and ethical manner.

We would greatly value your continued help. Thank you for considering this request.

<u>If you are interested in continuing to take part in the study, please confirm with either of us below.</u>

Audrey McKinlay (366 7001 Ext 7885)
Clinical Psychologist
PhD Candidate
Department of Psychology
University of Canterbury

John Dalrymple-Alford ("John D-A" 364 2998 or 366 7002 Ext. 6382).
Associate Professor
Department of Psychology
University of Canterbury

XXIV - Ethics Approval For Study Two

Canterbury
Ethics Committees
4th Floor, 250 Oxford Terrace
P.O. Box 3877
Christchurch
Fax (03) 372 1015

17 November 2004

Department of Psychology
University of Canterbury
Private Bag 4800
Christchurch

Attn: Audrey McKinlay

Developing cognitive measures for Parkinson's disease
Investigators: A/Prof J Dalrymple-Alford, Prof T Anderson, Dr J Fink, Prof P Barrett, Ms A McKinlay, P Kavanagh
Ethics Ref: CTB/04/09/158

Thank you for your response to the Committee's suggestions. The above study has now been given ethical approval by the Canterbury Ethics Committee.

Snip

General
It should be noted that Ethics Committee approval does not imply any resource commitment or administrative facilitation by any healthcare provider within whose facility the research is to be carried out. Where applicable, authority for this must be obtained separately from the appropriate manager within the organisation.

We wish you well with your study and would request that you quote the above ethics reference number in all correspondence and should any of the above approved documentation be revised in the future please ensure a new version number and/or date is also amended to assist the approval procedure.

Yours sincerely

Joanne Hamlyn
Ethics Committee B Administrator
Email: joanne_hamlyn@moh.govt.nz
Phone: (03) 372 3037

XXV - Consent Form Used For Study Two

Consent Form

<u>Project Title:</u> Developing cognitive measures for Parkinson's disease

I have been invited to take part in this study on cognition (including thinking and reasoning) and planning and decision making in people with Parkinson's disease. An information sheet has been provided on the aims and purpose of the study. I have read and understood the information it contained. I have been given an opportunity to discuss the study. I am satisfied with the answers that have been given. I have had time to consider whether to take part.

I understand that:

- Participation in the study is voluntary (my choice)
- I am free to withdraw from the study at any time and this will in no way affect my future healthcare.
- I am free to refuse to answer any questions that I do not want to answer.
- This study has approval from the Canterbury Ethics Committee.
- My participation in the study is confidential and no information that could identify me will be used in any reports that may be generated from this study.
- if any assessments raise concern about my health this will be conveyed to me and my General Practitioner
-

I have been provided with information regarding who to contact if I have any concerns regarding the study.

(PD patients only) My neurologist can be informed of my participation YES / NO

(All participants) I would like to receive a copy of the results of this study YES / NO

I _____ consent to take part in this study
(full name)

Signature:_____ Date: _____

<u>Researchers</u>: John Dalrymple-Alford PhD, Tim Anderson MD, John Fink MD, Paul Barrett PhD, Audrey McKinlay MA, Dip Clin psyc, Phillip Kavangh, research assistant.

<u>Contact phone number</u>: Audrey McKinlay (366 7001 Ext. 7885) or Dr. John Dalrymple-Alford ("John D-A" 364 2998 or 366 7002 Ext. 6382).

Project explained by:_____

Project role: _____

Signature: _____Date: _____

XXVI - Health Check List And Hallucination Questionnaire Used In Study Two

Health checklist and background for Parkinson's disease patients

(to be completed by investigator)

Today's Date:

Full Name:	Control match:
Date of birth:	GP:
Satisfactory / corrected vision: Yes / No and hearing: Yes / No	

Current medications, including dose:

Other Comments:

- ○ Major medical illness (cardiovascular; diabetes req insulin; severe migraine; other:)
- ○ Significant psychiatric illness requiring hospitalization (specify:)
- ○ Major depression in last 6 months
- ○ Dementia / hallucinations
- ○ Medications known to have a significant effect on CNS other than anti-PD medication

1) Which day(s) and time you are most likely to be free to take part in the study?_____

2) Caffeine drinks (e.g. coffee, tea, chocolate, caffeinated soft drinks)
Per day: None / Little (One cup or can per day)
Moderate (2 or 3)
Heavy (4 or more)
3) Alcohol Daily average (ALAC guide: Male amount shown below; half of this for women)

Per day: None / Little (less than moderate daily average)
Moderate (1/3 to 1 spirit;1-2.5 glass wine; or 2-5 glasses of beer; as a daily average)

Heavy (more than moderate daily average

Questions For Hallucinations
(Asked by Researcher)

Do you have any day-time sleepiness? Yes/No

If yes describe:

Do you every have any sudden falls/faintness? Yes/No

If yes explain:

Specific Questions if Hallucinations Pressent

Are they bought on by the medication? Yes/No

Are they present when you are moving? Yes/No

How frequently do you experience them? Daily/Weekly/Monthly

How long do they last?

What do you make of these episodes? (do they retain insight i.e do they know that these episodes are strange or bizarre?)

XXVII - Consent Form To Obtain Information From A Significant Other - Study Two

Consent to obtain additional information from my spouse, caregiver or "significant other" person

<u>Project Title:</u> Developing Cognitive measures for Parkinson's Disease

I agree that the researchers involved with this study may seek to obtain additional relevant information from the person named below. I understand that the information sought will cover aspects of my general daily functioning, including questions relating to my planning and decision making.

I have heard and understood an explanation of the reasons for wanting to obtain information from someone else about me. I have had an opportunity to ask questions and am satisfied with the answers I have been given.
I understand that:

- I may withdraw my consent at any time and this will in no way affect my future health care.
- Participation of the person I have nominated (below) is entirely voluntary (their choice).
- The information provided by this person will be strictly confidential and no information that could identify me will be used in any reports that may be generated from this study.
- That person is entirely free to refuse to answer any questions that they do not want to answer.
- This study has approval from the Canterbury Ethics Committee.

Signed:_____
Date:_____

Full name:
_____
(please print)

Name of person
nominated:_____

Relationship to
participant:_____

Signed consent by nominated
person_____

<u>Researchers</u>: John Dalrymple-Alford PhD, Tim Anderson MD, John Fink MD, Paul Barrett PhD, Audrey McKinlay MA, Dip Clin Psyc

Contact phone number: Audrey McKinlay (366 7001 Ext. 7885) or Dr. John Dalrymple-Alford ("John D-A" 364 2998 or 366 7002 Ext. 6382).

This form explained to participant by:_____

Project role:

_____

Signature: _____ Date:

_____

XXVIII - Overview Of Problem Selection And Tower Structures

Structure		Three Move		Four Move		Five Move		Six Move	
Goal Hierarchy[1]	Search Depth [2]	Start:Goal[3]	Sub-goal Pattern [4]	Start:Goal[3]	Sub-goal Pattern [4]	Start:Goal[3]	Sub-goal Pattern [4]	Start:Goal[3]	Sub-goal Pattern [4]
1	0	36:31	111						
1	0	56:51	111						
1	0	36:21	111						
1	0	56:41	111						
1	0	16:11	111						
2	0	12:34	111						
2	0	32:54	111						
1	1	54:61	011	14:51	0111				
1	1	42:31	011	34:11	0111				
1	1	64:51	011	54:31	0111				
1	1	62:51	011						
2	1	51:64	011						
2	1	14:63	011						
2	1	21:14	011			14:54	01011		
2	1	64:13	011			34:14	01011		
3	1					65:25	01011		
3	1					35:15	01011		
2	2					23:43	00111	33:14	001011
2	2					53:33	00111	43:64	001011
3	2							52:25	001011
3	2							62:35	001011
1	2					63:21	00111		
1	2					43:61	00111		
1	2					22:61	00111		
1	2					42:11	00111		
1	2					62:41	00111		
1	3							12:51	000111
1	3							62:21	000111
2	3							22:43	000111
2	3							52:33	000111

[1] Goal hierarchy 1=unambiguous, 2=partially ambiguous (see Kaller et al., 2004); [2] Search depth refers to the number of moves required prior to the first goal reaching move on the optimal solution path (Spitz et al. 1982);[3] Notation as suggested by Berg and Byrd (2002);[4]Sub-goal pattern refers to the sequence of moves, 0 = a sub-goal move and 1 = a goal move.

Goal Hierarchy			
	Partially ambiguous	Unambiguous	
With subgoals Search depth =1	P211 (2)	P111 (2)	With suboptimal alternatives
With subgoals Search depth = 1	P210 (2)	P110 (2)	No suboptimal alternatives
No subgoals Search depth = 0	P200 (2)	P100 (5)	No suboptimal alternative

Figue() Study design for phase one showing the manipulation of the structure of the tower problems. In the above table specific problems are referred to using a code of P and subsequent 3 digit number which denote problem classification. The first number indicates goal hierarchy (partially ambiguous = 2 and unambiguous=1) the second number refers subgoal (0=without sub-goal generation; 1=with sub-goal generation) and the third number to the presence of suboptimal alternatives (1= present, 0=absent) (notation suggested by Kaller et al 2004).

Table: Shows Structure and order of selected problems For Phase 1

No.	Problem[1]	In 1st Isoform [2]	Structure Type [3]	Moves	Subgoaling pattern [4]	Goal Hierarchy	Search Depth	Suboptimal alternatives	Respective moves for 1st isoform [5]
1	11:13	11:13	P200	1		2	0	0	11 13
2	26:34	16:64	P200	1		2	0	0	16 64
3	62:56	12:26	P200	2		2	0	0	12 25 26
4	31:45	11:25	P300	2		2	0	0	11 12 25
5	36:21	16:61	P100	3	- 111	1	0	0	16 64 63 61
6	32:54	12:34	P200	3	- 111	2	0	0	12 25 26 34
7	64:51	14:21	P110	3	- 011	1	1	0	14 15 22 21
8	21:14	11:24	P210	3	- 011	2	1	0	11 12 25 24
9	42:31	12:21	P111	3	- 011	1	1	1	12 25 23 21
10	14:63	14:63	P211	3	- 011	2	1	1	14 66 65 63
11	51:64	11:24	P210	3	- 011	2	1	0	11 12 25 24
12	12:34	12:34	P200	3	- 111	2	0	0	12 25 26 34
13	56:41	16:61	P100	3	- 111	1	0	0	16 64 63 61
14	64:13	14:63	P211	3	- 011	2	1	1	14 66 65 63
15	62:51	12:21	P111	3	- 011	1	1	1	12 25 23 21
16	54:61	14:21	P110	3	- 011	1	1	0	14 15 22 21

[1]Notation consistent with that suggested by Berg & Byrd (2002); [2] Isoform refers to the permutations of ball positions referred to by Berg & Berg (2002). The various arrangement or permutation of balls in each of the 6 isoforms are identical only the order of ball colors changes. Therefore, for the purpose of comparison each problem can be converted to a "1st isoform". [3] In the above table specific problems are referred to using a code of P and subsequent 3 digit number which denote problem classification. The first number indicates goal hierarchy (partially ambiguous = 2 and unambiguous=1) the second number refers subgoal (0=without sub-goal generation; 1=with sub-goal generation) and the third number to the presence of suboptimal alternatives (1= present, 0=absent) (notation suggested by Kaller et al 2004); [5] Sub-goal pattern refers to the sequence of moves, 0 = a sub-goal move and 1 = a goal move. [5] Sequence of moves required for the optimal solution path using notation suggested by Berg & Byrd (2002).

Goal Hierarchy

Unambiguous

With subgoals Search depth =1	P100 (3)	No suboptimal Alternatives
With subgoals Search depth = 2	P110 (3)	No suboptimal Alternatives
No subgoals Search depth = 3	P110 (3)	No suboptimal Alternatives

Figure() Study design for phase one showing the manipulation of the structure of the tower problems. In the above table specific problems are referred to using a code of P and subsequent 3 digit number which denote problem classification. The first number indicates goal hierarchy (unambiguous=1) the second number refers subgoal (0=without sub-goal generation; 1=with sub-goal generation) and the third number to the presence of suboptimal alternatives (1= present, 0=absent) (notation suggested by Kaller et al 2004).

Goal Hierarchy

	Ambiguous	Partially Ambiguous	Unambiguous	
Search Depth =1	P311 (2 x 5 move problems)	P211 (2 x 5 move problems)		With 2 Suboptimal Alternatives
Search Depth = 2	P311 (2 x 6 move problems)	P211 (2 x 6 move problems)		With 2 Suboptimal Alternatives
Search Depth = 2		P211 (2 x 5 move problems)	P111 (2 x 5 move problems)	With 1 Suboptimal Alternatives
Search Depth = 3		P211 (2 x 6 move problems)	P111 (2 x 6 move problems)	With 1 Suboptimal Alternatives

Figue() Study design for phase two showing the design for anaysing the effect of manipulation of the structure of the tower and number of moves across the problems. In the above table specific problems are referred to using a code of P and subsequent 3 digit number which denote problem classification. The first number indicates goal hierarchy (Ambiguous =3; partially ambiguous = 2 and unambiguous=1) the second number refers sub-goal (0=without sub-goal generation; 1=with sub-goal generation) and the third number to the presence of suboptimal alternatives (1= present, 0=absent) (notation suggested by Kaller et al 2004).

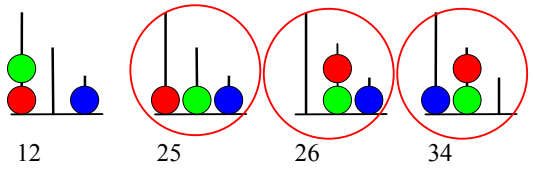
Table: Shows Structure and order of selected problems For Phase 2 section one and section 2 (indicated by bold line)

No.	Problem 1	In 1st isoform 2	Structure type 3	Moves	Subgoaling pattern 4	Goal Hierarchy	Search Depth	Suboptimal alternatives	Respective moves for 1st isoform
17	56:51	16:11	P100	3	-111	1	0	0	16 15 13 11
18	34:11	14:51	P110	4	0111	1	1	0	14 66 65 52 51
19	62:41	12:31	P110	5	00111	1	2	0	12 25 26 34 33 31
20	36:31	16:11	P100	3	-111	1	0	0	16 15 13 11
21	14:51	14:51	P110	4	0111	1	1	0	14 66 65 52 51
22	22:61	12:31	P110	5	00111	1	2	0	12 25 26 34 33 31
23	16:11	16:11	P100	3	-111	1	0	0	16 15 13 11
24	54:31	14:51	P110	4	0111	1	1	0	14 66 65 52 51
25	42:21	12:31	P110	5	00111	1	2	0	12 25 26 34 33 31
26	63:21	13:51	P111	5	00111	1	2	1	13 14 66 65 52 51
27	23:43	13:53	P211	5	00111	2	2	1	13 14 66 65 52 53
28	34:14	14:54	P211	5	01011	2	1	2	14 66 65 52 53 54
29	65:25	15:55	P311	5	01011	3	1	2	15 16 64 63 62 55
30	43:61	13:51	P111	5	00111	1	2	1	13 14 66 65 52 51
31	53:33	13:53	P211	5	00111	2	2	1	13 14 66 65 52 53
32	14:54	14:54	P211	5	01011	2	1	2	14 66 65 52 53 54
33	35:15	15:55	P311	5	01011	3	1	2	15 16 64 63 62 55
34	62:21	12:51	P111	6	000111	1	3	1	12 13 14 66 65 52 51
35	22:43	12:53	P211	6	000111	2	3	1	12 13 14 66 65 52 53
36	33:14	13:54	P211	6	001011	2	2	2	13 14 66 65 52 53 54
37	52:25	12:45	P311	6	001011	3	2	2	12 25 26 34 33 32 45
38	12:51	12:51	P111	6	000111	1	3	1	12 13 14 66 65 52 51
39	52:33	12:53	P211	6	000111	2	3	1	12 13 14 66 65 52 53
40	43:64	13:54	P211	6	001011	2	2	2	13 14 66 65 52 53 54
41	62:35	12:45	P311	6	001011	3	2	2	12 25 26 34 33 32 45

[1] Notation consistent with that suggested by Berg & Byrd (2002); [2] Isoform refers to the permutations of ball positions referred to by Berg & Berg (2002). The various arrangement or permutation of balls in each of the 6 isoforms are identical only the order of ball colors changes. Therefore, for the purpose of comparison each problem can be converted to a "1st isoform". [3] In the above table specific problems are referred to using a code of P and subsequent 3 digit number which denote problem classification. The first number indicates goal hierarchy (partially ambiguous = 2 and unambiguous=1) the second number refers subgoal (0=without sub-goal generation; 1=with sub-goal generation) and the third number to the presence of suboptimal alternatives (1= present, 0=absent). (notation suggested by Kaller et al 2004); [5] Sub-goal pattern refers to the sequence of moves, 0 = a sub-goal move and 1 = a goal move. [6] Sequence of moves required for the optimal solution path using notation suggested by Berg & Byrd (2002).

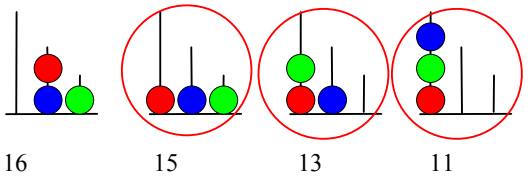
3 Move Problems - **Optimal Path** (asterix indicate problems used)
subgoaling pattern 111. Red circles indicate goal moves.

Problem type 1



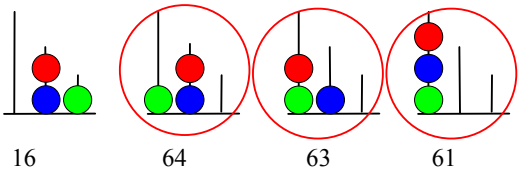
Isoforms 12:34*
22:64
32:54*
42:24
52:14
62:44

Problem type 2



Isoforms 16:11*
26:21
36:31*
46:41
56:51*
66:61

Problem type 3

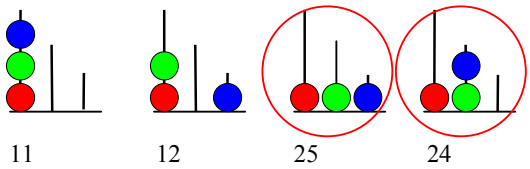


Isoforms 16:61
26:31
36:21*
46:51
56:41*
66:11

---

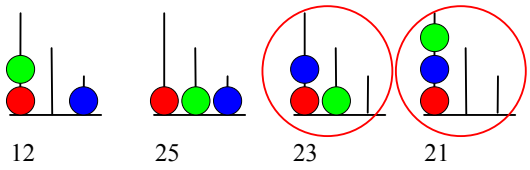
3 Move Problems - **Optimal Path** (asterix indicate problems used)
subgoaling pattern 011. Red circles indicate goal moves.

Problem type 1



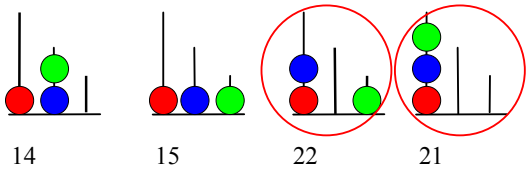
Isoforms 11:24
21:14*
31:44
41:34
51:64*
61:54

Problem type 2



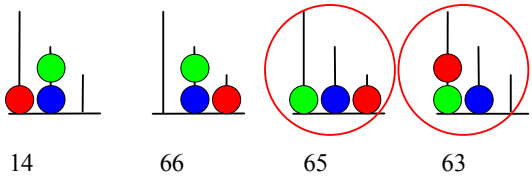
Isoforms 12:21
22:11
32:41
42:31*
52:61
62:51*

Problem type 3



Isoforms 14:21
24:11
34:41
44:31
54:61*
64:51*

Problem type 4.

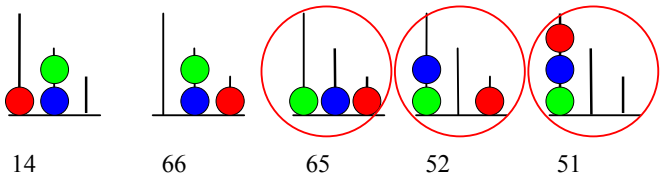


Isoforms 14:63*
24:33
34:23
44:53
54:43
64:13*

---

4 Move Problems - **Optimal Path** (asterix indicate problems used)
subgoaling pattern 0111. Red circles indicate goal moves.

Problem type 1



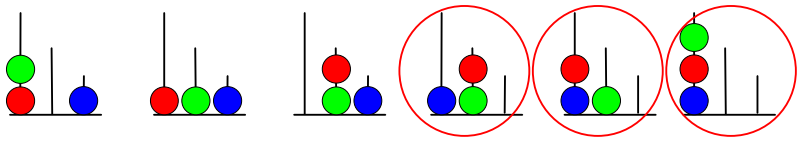
14 66 65 52 51

Isoforms 14:51*
24:41
34:11*
44:61
54:31*
65:21

---

5 Move Problems - **Optimal Path** (asterix indicate problems used)
subgoaling pattern 00111. Red circles indicate goal moves.

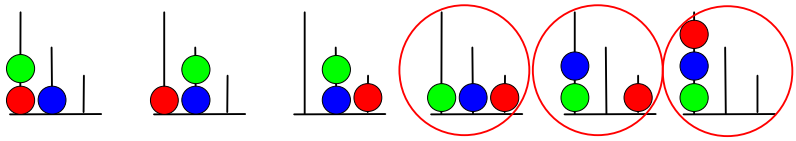
Problem type 1



12 25 26 34 33 31

Isoforms 12:31*
22:61*
32:51
42:21
52:11
62:41*

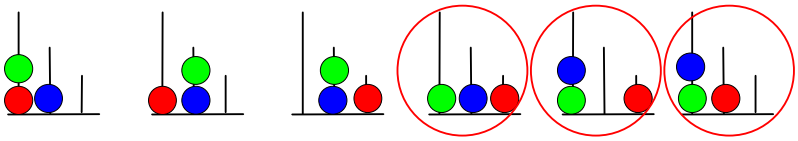
Problem type 2



13 14 66 65 52 51

Isoforms 13:51
23:41
33:11
43:61*
53:31
63:21*

Problem type 3



13 14 66 65 52 53

Isoforms 13:53
23:43*
33:13
43:63
53:33*
63:23

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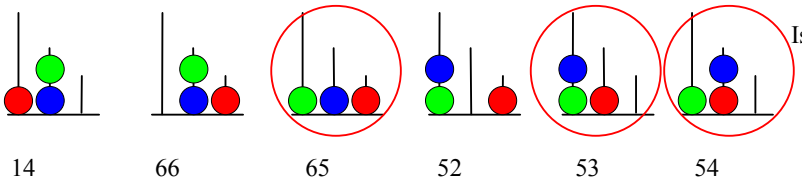
5 Move Problems - **Optimal Path** (asterix indicate problems used)
subgoaling pattern 01011. Red circles indicate goal moves

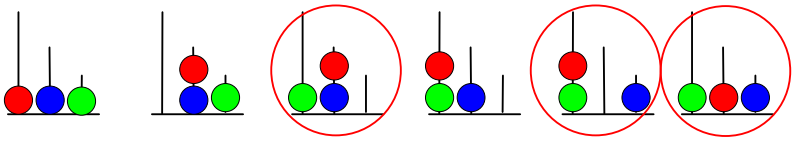
Problem type 1.



14 66 65 52 53 54

Isoforms 14:54*
24:44
34:14*
44:64
54:34
64:24

Problem type 2.



15 16 64 63 62 55

Isoforms 15:55
25:45
35:15*
45:65
55:35
65:25*

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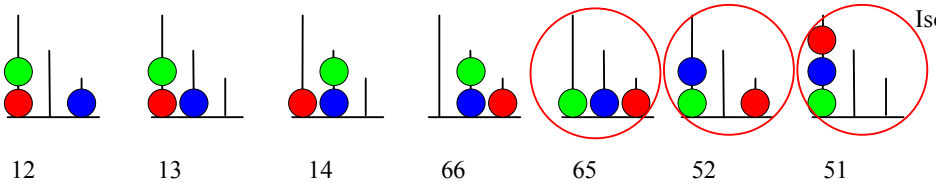
6 Move Problems - **Optimal Path (** asterix indicate problems used)
subgoaling pattern 000111. Red circles indicate goal moves.

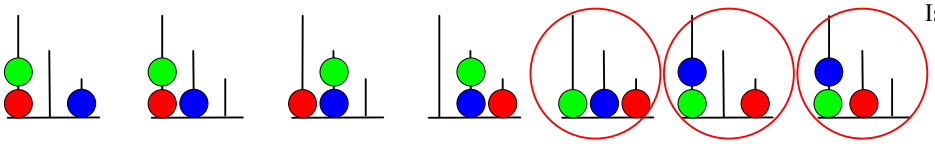
Problem type 1



12 13 14 66 65 52 51

Isoforms 12:51*
22:41
32:11
42:61
52:31
62:21*

Problem type 2



12 13 14 66 65 52 53

Isoforms 12:53
22:43*
32:13
42:63
52:33*
62:23

XXIX - Full Analysis For Regression Outcomes – Language And Parkinson's Disease

Table 1: Results of regression analysis, where the Total Score on the PDQ-39 is used as the Dependent variable. Results displayed show incremental change accounted for by each neuropsychiatric symptom (R^2 change) after controlling for motor symptoms (tremor, non tremor scores).

Independent Variables	**Beta**	***B***	**Std. Err. Of *B***	***t***	***p***				
Tremor	0.06	1.97	4.29	0.46	>0.60				
Non Tremor	0.61	20.48	4.07	0.04	<0.001				
Variables Entered						***F*-value**	**R^2**	**R^2 change**	***p***
Anxiety						59.17	0.71	0.46	<0.001
Apathy						3.21	0.43	0.04	<0.10
Fatigue						2.96	0.43	0.04	<0.10
Depression						26.15	0.62	0.23	<0.001
Sleep						1.71	0.41	0.02	>0.15
Hallucinations						8.62	0.49	0.10	<0.001

Table 2: Results of a regression analysis, where ratings on the sub-scale "Mobility" from the PDQ-39, is used as the dependent variable. Results displayed show incremental change accounted for by each neuropsychiatric symptom (R^2 change) after controlling for motor symptoms (tremor, non tremor scores).

Independent Variables	**Beta**	***B***	**Std. Err. Of *B***	***t***	***p***				
Tremor	-0.10	-5.52	6.13	-0.90	>0.35				
Non Tremor	0.71	37.72	5.82	6.49	<0.0001				
Variables Entered						***F*-value**	***R*^{2}**	***R*^{2} change**	***p***
Anxiety						15.43	0.55	0.18	<0.001
Apathy						0.00	0.48	0.00	>0.90
Fatigue						2.39	0.51	0.26	>0.10
Depression						7.19	0.55	0.07	<0.02
Sleep						0.09	0.48	0.00	>0.77
Hallucinations						2.92	0.51	0.03	<0.10

Table 3:Results of a regression analysis, where ratings on the sub-scale "Bodily Discomfort" from the PDQ-39, is used as the dependent variable. Results displayed show incremental change accounted for by each neuropsychiatric symptom (R^2 change) after controlling for motor symptoms (tremor, non tremor scores).

Independent Variables	**Beta**	***B***	**Std. Err. Of *B***	***t***	***p***
Tremor	0.03	1.71	7.55	0.23	>0.80
Non Tremor	0.39	20.26	7.16	2.83	<0.01

Variables Entered	***F*-value**	***R*²**	***R*² change**	***p***
Anxiety	11.23	0.26	0.22	<0.01
Apathy	0.10	0.17	0.00	>0.70
Fatigue	3.28	0.22	0.06	<0.10
Depression	4.53	0.24	0.08	<0.05
Sleep	2.27	0.20	0.04	>0.10
Hallucinations	7.66	0.28	0.12	<0.01

Table 4: Results of a regression analysis, where ratings on the sub-scale "Cognitive Impairment" from the PDQ-39, is used as the dependent variable. Results displayed show incremental change accounted for by each neuropsychiatric symptom (R^2 change) after controlling for motor symptoms (tremor, non tremor scores).

Independent Variables	**Beta**	***B***	**Std. Err. Of *B***	***t***	***p***
Tremor	0.23	9.62	5.16	1.87	<0.10
Non Tremor	0.48	18.69	4.88	3.83	<0.001

Variables Entered	***F*-value**	R^2	R^2 **change**	***p***
Anxiety	31.37	0.62	0.32	<0.0001
Apathy	7.41	0.44	0.09	<0.01
Fatigue	7.43	0.44	0.09	<0.01
Depression	14.67	0.51	0.16	<0.001
Sleep	0.08	0.34	0.00	>0.75
Hallucinations	8.89	0.45	0.11	<0.01

Table 5: Results of a regression analysis, where ratings on the sub-scale "Social Support" from the PDQ-39, is used as the dependent variable. Results displayed show incremental change accounted for by each neuropsychiatric symptom (R^2 change) after controlling for motor symptoms (tremor, non tremor scores).

Independent Variables	**Beta**	***B***	**Std. Err. Of *B***	***t***	*p*
Tremor	0.15	4.33	4.17	1.04	>0.30
Non Tremor	0.36	9.93	3.95	2.51	<0.05

Variables Entered	***F*-value**	R^2	R^2 **change**	***p***
Anxiety	7.57	0.23	0.16	<0.01
Apathy	0.89	0.19	0.02	>0.30
Fatigue	2.66	0.22	0.05	>0.10
Depression	3.58	0.24	0.06	<0.10
Sleep	1.13	0.19	0.02	>0.25
Hallucinations	0.43	0.18	0.01	>0.50

Table 6: Results of a regression analysis, where ratings on the sub-scale "Communication difficulties" from the PDQ-39, is used as the dependent variable. Results displayed show incremental change accounted for by each neuropsychiatric symptom (R^2 change) after controlling for motor symptoms (tremor, non tremor scores).

Independent Variables	**Beta**	***B***	**Std. Err. Of *B***	***t***	***p***				
Tremor	0.07	3.68	7.13	0.52	>0.60				
Non Tremor	0.49	24.66	6.75	3.65	<0.001				
Variables Entered						***F*-value**	***R*²**	***R*² change**	***p***
Anxiety						7.20	0.30	0.14	<0.02
Apathy						10.31	0.40	0.14	<0.01
Fatigue						0.38	0.26	0.01	<0.50
Depression						4.98	0.33	0.08	<0.05
Sleep						3.37	0.31	0.05	<0.10
Hallucinations						3.88	0.32	0.06	<0.06

Table 7: Results of a regression analysis, where ratings on the sub-scale "Activities of Daily Living" from the PDQ-39, is used as the dependent variable. Results displayed show incremental change accounted for by each neuropsychiatric symptom (R^2 change) after controlling for motor symptoms (tremor, non tremor scores).

Independent Variables	**Beta**	***B***	**Std. Err. Of *B***	***t***	***p***				
Tremor	0.14	6.74	5.73	1.18	>0.20				
Non Tremor	0.60	28.28	5.44	5.20	<0.0001				
Variables Entered						***F*-value**	**R^2**	**R^2 change**	***p***
Anxiety						8.86	0.44	0.13	<0.01
Apathy						7.02	0.50	0.08	<0.02
Fatigue						5.42	0.49	0.06	<0.05
Depression						5.18	0.48	0.06	<0.05
Sleep						3.59	0.47	0.04	<0.10
Hallucinations						6.13	0.49	0.07	<0.02

Table 8: Results of a regression analysis, where ratings on the sub-scale "Stigma" from the PDQ-39, is used as the dependent variable. Results displayed show incremental change accounted for by each neuropsychiatric symptom (R^2 change) after controlling for motor symptoms (tremor, non tremor scores).

Independent Variables	**Beta**	***B***	**Std. Err. Of *B***	***t***	***p***
Tremor	0.14	7.36	7.62	0.97	>0.30
Non Tremor	0.60	7.28	7.23	1.01	>0.30

Variables Entered	***F*-value**	R^2	R^2 **change**	***p***
Anxiety	10.29	0.25	0.20	<0.01
Apathy	1.87	0.90	0.04	>0.15
Fatigue	0.07	0.06	0.00	>0.75
Depression	5.86	0.16	0.11	<0.02
Sleep	0.91	0.07	0.02	>0.30
Hallucinations	2.33	0.10	0.05	>0.10

Table 9: Results of a regression analysis, where ratings on the sub-scale "Emotion" from the PDQ-39, is used as the dependent variable. Results displayed show incremental change accounted for by each neuropsychiatric symptom (R^2 change) after controlling for motor symptoms (tremor, non tremor scores).

Independent Variables	**Beta**	***B***	**Std. Err. Of *B***	***t***	***p***				
Tremor	0.03	1.36	6.36	0.21	>0.80				
Non Tremor	0.33	13.82	6.04	2.29	<0.05				
Variables Entered						***F*-value**	***R*^{2}**	***R*^{2} change**	***p***
Anxiety						61.31	0.63	0.60	<0.0001
Apathy						2.01	0.15	0.04	>0.15
Fatigue						1.82	0.15	0.03	>0.15
Depression						39.50	0.53	0.41	<0.0001
Sleep						0.92	0.13	0.02	>0.30
Hallucinations						9.59	0.27	0.16	<0.01