



Cognitive Reserve in Parkinson's Disease

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Declaration of Originality

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The research conducted in this thesis abides by the Australian codes on human and animal experimentation. Approval for this study was obtained from the Health and Medical Human Research Ethics Committee of the University of Tasmania.

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Declaration of Interests

No competing or conflicting interests need to be declared for the studies contained in this thesis.

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Abstract

Parkinson's Disease is among the most common neurodegenerative disease affecting individuals worldwide. In addition to the motor symptoms that are present in the disease there are significant cognitive impairments that people with Parkinson's Disease experience as part of the disease process that cause significant disability. The concept of protective factors against cognitive decline, known as cognitive reserve, have been investigated and demonstrated in other dementia populations. These indicators include pre-morbid IQ, education level and participation in lifestyle activities. This study aimed to investigate whether cognitive reserve is present in people with Parkinson's Disease, with consideration given to existing measures and the influence of mood disorders on cognition in the population.

88 Participants were administered a comprehensive neuropsychological battery including overall and specific cognitive function measures, pre-morbid IQ, lifestyle activity participation, mood and demographic factors. Cognitive decline scores were calculated by comparison of current and pre-morbid IQ scores and these compared to potential cognitive reserve measures and mood factors.

Previously identified indicators of cognitive reserve were not confirmed in the results, though the regular playing of musical instruments was identified as a potential factor for further investigation. Pre-morbid IQ and education demonstrated an increase in decline rather than a decrease which is attributed to Wilder's law of initial values. Mood factors were shown to affect cognition in the Parkinson's Disease population highlighting their importance in the treatment of the disease.

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Chapter 1: Overview of the Thesis

Parkinson's Disease (PD) is the second most common neurological disorder in Australia, affecting more than 64,000 individuals. The disease is both disabling and degenerative with affected individuals requiring increasing levels of assistance with Activities of Daily Living (ADLs) and supported accommodation later in life. PD has both physical and cognitive symptoms and while the physical symptoms are more recognised for their disabling effects, the cognitive symptoms can be equally severe and can adversely affect the individual's ability to cope with their changing physical abilities.

The progression of the cognitive aspects of PD is poorly understood, likely in part due to the focus on treating the physical symptoms of the disease. Understanding the progression of the cognitive aspects of disease, and identifying any factors that may be predictive or preventative in the development of these cognitive impairments, could add valuable information to the treatment plans of individuals with the condition.

This research examines cognitive impairments in individuals with PD. It examines the possible influence on current cognition in a PD population of three key factors: pre-morbid functioning, participation in lifestyle activities, and mood. The research examines whether these three factors appear to have any protective or predictive influence in the development of cognitive deficits in individuals with PD. Each of these three factors is investigated via comparison of current cognitive function (measured using the Repeatable Battery for the Assessment of Neuropsychological Status; RBANS) with a measure of pre-morbid function (the National Adult Reading Test; NART). By examining the level of cognitive decline present in groups which vary on each of the three factors, it is possible to investigate the effect that each of these has on both current level of functioning and changes in functioning over the course of the disease.

Identification of pre-morbid, lifestyle or mood based factors that affect performance on cognitive tasks may demonstrate that PD is not a singular progression path, but rather is treatable through therapeutic programmes targeting associated conditions (such as anti-depressant medication). It is hoped that this, in turn, may lead to an ability to improve the overall quality of life of people with the disease.

Chapter 2: Introduction to Parkinson's Disease

2.1 Parkinson's Disease

Parkinson's Disease (PD) is a chronic, progressive neurological condition of largely unknown aetiology. It is estimated to be the second most common neurological disorder, after Alzheimer's Disease, and is said to affect 1-2% of the population aged sixty and above (de Lau and Breteler, 2006). The condition is characterised by the cardinal symptoms; bradykinesia, resting tremor, rigidity and postural instability. Although two of these symptoms are needed for a diagnosis to be made, many individuals become conscious of the disease by the presence of a unilateral or bilateral tremor. While PD is generally recognised for its motor symptoms, there exist many non-motor manifestations of the disease including cognitive, sensory and autonomic disturbances (Albanese, 2003). Cognitive dysfunctions that occur as a result of PD can often be as debilitating as the motor disturbances, but their impact is less understood.

2.2 Epidemiology

A 2005 study estimated that there were between 4.1 million and 4.6 million individuals with PD in the most populous countries of the world, with that figure expected to rise to between 8.7 million and 9.3 million by 2030 (Dorsey et al., 2005). A 2011 study reviewed previous estimates of the prevalence of PD and concluded that it was too difficult to give an accurate estimate of worldwide incidence due to reporting differences between countries (Muangpaisan, Mathews, Hori & Seidel, 2011).

An Australian government report (2011) estimates that there are currently 64,000 individuals in Australia living with PD of which 52% are male and 48% female. It also reports that approximately 3962 of these individuals are aged between 35 and 54 years old

and 80% are over the age of 65. It is also reported that 12,000 individuals with PD are of working age meaning that early and effective detection of the cognitive deficits in PD are crucial to determine so that these individuals can obtain tailored support to assist them stay in the workforce.

2.3 Early-Onset Parkinson's Disease

PD is a degenerative condition that is diagnosed by clinical observation of expressed symptomatology. As such, it is typically diagnosed in older individuals, with the majority of diagnoses occurring over the age of 60. However some people develop symptoms substantially earlier (<55 years) and are diagnosed with the sub-condition known as Early Onset Parkinson's Disease.

Research has shown that people who develop early onset PD tend to respond better to anti-Parkinsonian medication than those who commence treatment in their sixties or older (Wickremaratchi, Ben-Shlomo & Morris, 2009). Unfortunately, however, these individuals tend to be at an increased risk of developing dyskinesias as a result of long term medication use (Giovannini et al., 1991; Wickrematchi et al., 2009). Those who develop early onset PD experience slower disease progression than their older counterparts, both physically and cognitively (Wickrematchi et al., 2009). However they tend to experience worse outcomes long term, with higher incidence of symptoms such as dementia that can lead to increased disability and mortality rates (Wickremaratchi et al., 2009).

2.4 Diagnosis

PD is often interpreted as referring to a cluster of conditions rather than a single disease entity (Tolosa, Wenning & Poew, 2006). Currently, there are no medical based

tests that can definitively diagnose a living individual with PD; PD can only be accurately diagnosed through examination of neurological pathology, generally post mortem (Lee, Williams & Storey, 2012). As such, the diagnosis of PD relies primarily on the assessment of clinical findings (de Lau & Breteler, 2006). A diagnosis by clinical examination requires a clinician to observe a resting tremor as well as at least two of bradykinesia, cogwheel rigidity or postural abnormalities (Aarsland et al., 2001). In some cases clinicians will also test for a response to a dopaminergic agent, such as Levodopa, as an indicator for diagnosis (Aarsland et al., 2001).

PD presents as a cluster of symptoms that can often vary from person to person, both in terms of symptom cluster and symptom severity. This results in a lack of clarity surrounding diagnosis and, as such, interpretation of diagnostic criteria can differ between clinicians (Lee, Williams & Storey, 2012). This difference can be emphasised depending on whether the clinician is assessing solely for idiopathic PD or include symptoms of a Parkinsonian type condition in their diagnosis. Studies have found that because of this lack of clarity and consistency between clinicians the diagnostic error can occur in up to 20% of people with PD (Albanese, 2003).

2.4.1 Differential Diagnoses

Parkinsonian features can occur as a result of many conditions making it important for clinicians to differentiate between PD and other conditions with symptom overlap when making a diagnosis. Essential tremor, multi-system atrophy, progressive supranuclear palsy, and cortico-basal degeneration all share symptoms with PD (Tolosa, Wenning & Poewe, 2006).

The accurate diagnosis of PD is crucial in order to allow the correct treatment to be initialised for those who experience from the condition. This makes investigations into

methods of consistent and accurate identification of the disease imperative in order to continue to develop best practice treatment regimens and techniques.

2.4.2 Imaging Techniques

Although most clinicians have access to imaging techniques such as computerised tomography (CT) or magnetic resonance imaging (MRI) to assist with diagnosis, to date there are no clinical hallmarks that appear on this type of scanning (de Lau & Breteler, 2006). At best these scans can be used for the purposes of ruling out differential diagnoses, assessing cerebral atrophy and assessing age related brain changes (Hirano, Shintoh & Eidelberg, 2012; Tolosa et al., 2006). The cost of these techniques, along with their inability to definitively diagnose the disease, means that they are infrequently utilised in diagnosis of PD.

Individuals with PD can occasionally demonstrate a MRI signal void in the substantia nigra (Tolosa et al., 2006). However, this tends to be detectable only by using high field MRI scanners which are expensive to use and unavailable to most clinicians (Tolosa et al., 2006). Single photon emission computerised tomography (SPECT) and positron emission tomography (PET) have emerged in clinical practice as more useful ways of imaging those with suspected PD, as they carry with them the ability to examine neuro-chemical brain changes (Tolosa et al., 2006). However, like their imaging counterparts, these techniques are generally inconclusive and expensive to perform (Tolosa et al., 2006).

2.4.3 Diagnostic Instruments

Several diagnostic criteria and staging instruments used in the assessment of PD exist including the Hoehn and Yahr Scale, demonstrated in Figure 1, and the Unified Parkinson's Disease Rating Scale (UPDRS). These scales rate the level of impairment in

those with PD with the first levels of both scales representing early stage disease and the last later stage disease processes. Those with idiopathic PD can be benchmarked against either scale with the UPDRS being more commonly employed in current clinical practice.

Stage Hoehn and Yahr Scale		Modified Hoehn and Yahr Scale
1	Unilateral involvement only usually with minimal or no functional disability	Unilateral involvement only
1.5	-	Unilateral and axial involvement
2	Bilateral or midline involvement without impairment of balance	Bilateral involvement without impairment of balance
2.5	-	Mild bilateral disease with recovery on pull test
3	Bilateral disease: mild to moderate disability with impaired postural reflexes; physically independent	Mild to moderate bilateral disease; some postural instability; physically independent
4	Severely disabling disease; still able to walk or stand unassisted	Severe disability; still able to walk or stand unassisted
5	Confinement to bed or wheelchair unless aided	Wheelchair bound or bedridden unless aided

Figure 1. Hoehn and Yahr Scale

The employment of such rating scales and diagnostic criteria is imperative in ensuring correct and consistent diagnosis of PD across clinicians. In turn, it is essential for correct management of people with PD as several similar disease processes can closely represent PD.

2.5 Causes and Risk Factors

The most recognised risk factor in development of PD is a genetic component. Many studies have shown that those with a family history of PD are at higher risk of developing the condition (de Lau & Breteler, 2006). However, the hereditary link is not definitive; some individuals develop PD without a familial history, and some people with PD have children who do not develop the condition.

Other risk factors have been investigated for PD, with many studies having shown that pesticide exposure may be a causative risk for the condition. The majority of studies examining pesticide exposure, however, are flawed due to the inability to isolate single toxins due to concomitant exposures and the fact that studying pesticide exposure relies heavily on individual recall (Hubble, Cao, Hassanein, Neuberger & Koller, 1993).

De Lau and Breteler (2006) reported that drinking coffee and smoking tobacco may lower the risk of developing PD. Nicotine has been shown to force the release of dopamine, thus acting in a neuro-protective manner against the development of PD. The long term use of dopamine agonists such as anti-emetics or antipsychotic medication has also been shown to induce Parkinsonism due to their anti-cholinergic effects (Tolosa et al., 2006).

2.6 Pathophysiology

Parkinson's Disease is thought to develop due to neuronal loss in the substantia nigra and the development of Lewy bodies (de Lau & Breteler, 2006). Dopaminergic neurons are primarily found in the ventral tegmental area (VTA) of the midbrain, substantia nigra pars compacta, and arcuate nucleus of the hypothalamus (Ceravola, Rossie, Kiferle & Bonuccelli, 2010). Thus depletion of these neurons can lead to insufficient formation and

action of dopamine in the basal ganglia. In turn this leads to under-stimulation of the motor cortex and associated, characteristic motor symptoms recognised as “Parkinsonism”.

The basal ganglia play an important function in both motor activity and cognition. In each case they act as a decision making gateway in the brain allowing the translation of internal decision to active outcomes. Chiefly they allow or suppress the transmission of actions to further parts of the brain; in a healthy brain they allow appropriate actions to occur and inappropriate actions to be suppressed (Koziol & Budding, 2009). In people with Parkinson’s Disease, however, suppression by the basal ganglia of unwanted or inappropriate signals may be impaired, leading to both motor and cognitive symptoms. In the motor context, such symptoms include difficulty commencing an activity (such as walking) or inability to stop a movement once it has begun, resulting in tremor. Similar problems in starting and stopping may be seen in cognitive functioning too (Koziol & Budding, 2009). Maintaining attention, for example, requires focusing on a salient stimulus while at the same time suppressing distracting actions. In a person with PD attention may be poorly modulated resulting, for instance, in difficulty maintaining attention on a book being read because of constant distraction to a bird at the window. Similarly, inability to selectively encourage and suppress appropriate and inappropriate actions respectively can result in unwanted action, even after a conscious decision against that action. In such cases the brain may be able to determine an appropriate course of action based on information but be unable to suppress contra-indicated action. Thus, regardless of the decision that takes place in the brain the outward expression of that decision may be inappropriate (Koziol & Budding, 2009).

The reduced dopamine action in the basal ganglia seen in Parkinson’s Disease, then, impedes the brain’s ability to encourage and suppress actions, both in the motor

sense and the cognitive sense. This can be observed in the expressed symptoms of the disease.

2.7 Symptoms of Parkinson's Disease

2.7.1 *Motor Symptoms*

The motor symptoms of PD include tremor at rest, muscle rigidity, slowed movement (bradykinesia) and shuffling gait (de Lau & Breteler, 2006). People with PD can sometimes have great difficulty in commencing a physical activity and may require assistance in commencing some activities. These symptoms represent the underlying brain physiology described in the previous section. Muscle rigidity, for example, is representative of the inability to suppress the inappropriate action of tensing the muscles while at the same time encouraging the appropriate action of relaxing the muscles. The inappropriate action is therefore sent to the fronto-striatal cortex and the muscle remains rigid despite the person's will to relax it.

The motor symptoms of PD have received much of the attention given to the disease and its treatment because they can be very physically disabling for the person. As the disease progresses it becomes more and more difficult for the individual to perform desired motor actions and hence they become less physically mobile and require increasing assistance to perform activities of daily living.

2.7.2 *Non-Motor Symptoms*

Although PD is primarily diagnosed by its motor symptoms, many non-motor symptoms also occur. Non-motor symptoms have a huge impact on both people with PD and their families but may be over-shadowed by physical symptoms and, as a result, are often overlooked (Breen & Druyte, 2013). Untreated, this can lead to both stress and the

development of psychological conditions, not only in those who have the disease but also their care-givers, friends and family. Non-motor symptoms, then, are a major contributor to reduction in quality of life for people who experience PD and their carer's and families, and hence examining and diagnosing non-motor issues is crucial in order to allow appropriate education and treatment to take place (Hinnell et al., 2012 in Breen & Druyte, 2013). This in turn means that developing more comprehensive ways of diagnosing and predicting outcomes for affected individuals is paramount to ensure that those with PD are well informed and receive appropriate treatment.

Common non-motor symptoms include mood disturbance, particularly anxiety and depression, and psychiatric disturbances such as hallucinations and delusions. Fatigue is also common in the PD population. Other physical manifestations of the disease can also occur including worsening pain, bowel and urinary incontinence, sexual dysfunction, dizziness, fainting and drooling. These symptoms worsen with the progression of the disease as the control and perception of the relevant muscles worsens.

A substantial number of people with PD also experience some kind of cognitive disturbance as a result of their condition (Klepac, Trkulja, Relja & Babic, 2008). Cognitive problems can range from specific cognitive deficits, to mild cognitive impairment (MCI) to a Parkinson's Disease Dementia (PDD). Cognitive disturbances experienced in PD are discussed further in Chapter 3.

Chapter 3: Cognition and Parkinson's Disease

Although the more well-known symptoms of Parkinson's Disease (PD) are the motor symptoms, many people with PD also experience dementia or other cognitive dysfunction. It is estimated that as many as 90% of people with PD experience some sort of cognitive impairment (Dubois et al., 1991 in Montel & Bungener, 2008). Research into PD suggests that the disease can impact on numerous cognitive domains, including memory, language, attention, visuospatial, visuoconstructional and executive dysfunction (Hanna-Pladdy, Jones, Cabanban, Pahwa & Lyons, 2013; Kudlicka, Clare & Hindle, 2011).

Deficits arising from PD primarily occur in the domains of executive functioning and attention, accompanied frequently by impairment in cortical driven areas such as the memory, language and visuospatial functions; areas that are often affected in dementia of the Alzheimer's type (Litvan et al., 2011). This constellation of symptoms present in PD, with particular relevance given to executive dysfunction and attention deficits, is representative of a sub-cortical syndrome as seen in conditions such as Huntington's Disease (HD) and Multiple Sclerosis (MS) (Litvan et al., 2011).

3.1 Cognitive Domains Affected in PD

3.1.1 Executive functioning

Executive functions can be defined as 'mental processes involved in goal directed behaviour' (Marinus et al., 2003) or capacities that enable successful 'independent, purposive, self-serving behaviour' (Lezak, Howieson & Loring, 2004, page 34). Executive dysfunction is common in a variety of neurological conditions and typically leads to deficits in volition, planning, problem solving, purposive action and effective performance (Kudlicka et al., 2011).

A systematic review of executive function in PD revealed that executive function deficits are present in 31% of people with PD and that these deficits occur across all areas of executive function (Montel & Bungener, 2008). This incidence rate may be under-reported due to difficulties in accurately assessing executive functioning abilities, particularly based on observational assessment or clinical interview. A difficulty in measuring executive functioning well noted in many empirical studies is that the interpretation of measures is inconsistent (Kudlicka et al., 2011). Within structured settings overt cognitive difficulties seldom appear to exist whereas in new or everyday situations impairment in task management, planning, monitoring and attention and inhibition may become apparent, and this may affect self-reporting or reporting of symptoms by others who typically see the individual in familiar environments (Kudlicka et al., 2011).

It is postulated that in PD dopaminergic depletion leads to the disruption of communication between the basal ganglia and the fronto-striatal circuits which, in turn, affect the frontal lobes and lead to deficits in higher level functioning (Kozioł & Budding, 2009). Deficits in executive function are a plausible, even expected, expression of this pathology, with the basal ganglia unable to suppress or encourage inappropriate or appropriate responses to a set of stimuli (Kozioł & Budding, 2009).

One interesting aspect of executive dysfunction in individuals with PD is that they experience quite pronounced problems with internally guided behaviour while externally guided behaviour often remains intact (Marinus et al., 2003). Internally guided behaviour is initiated by the individual while externally guided behaviour is driven by external stimuli. Thus many people with PD do not initiate or begin tasks and activities in everyday living, but respond well to externally provided cues and prompts.

The ramifications of executive dysfunction on activities of daily living (ADLs) are well documented and can lead to increased disability, carer burden and health care costs

making it imperative to take into account executive function impairment in PD (Kudlicka et al., 2011). Executive dysfunction has been shown to decrease coping strategies. For instance Montel and Bungener (2008) demonstrated that people with PD associated executive dysfunction utilised more passive coping strategies than active coping strategies compared with a cognitively intact population due to deficits in mental flexibility. The authors also concluded that executive dysfunction led to greater social and occupation dysfunction in the affected population (Montel & Bungener, 2008).

Executive function deficits are usually the first cognitive problem to be identified in people with PD (Lee et al., 2013), though some studies have identified the executive dysfunction much later, in older people, with longer disease durations (Montel & Bungener, 2008). Kudlicka, Clare and Hindle (2013) suggested that the attentional aspects of executive function impairment can appear in milder forms of PD, but the difficulties in abstract reasoning occur only in more serious cases. This could be a reason for this conjecture around the incidence of executive functions in the disease depending on which aspects of executive function the instruments used measure. They are a hallmark cognitive symptom of sub-cortical conditions and as such their study in the PD population is crucial.

3.1.2 *Attention*

Attention is that set of cognitive functions which directs and maintains cognitive resources toward salient stimuli while excluding non-salient distractors. It is a key component in planning and problem solving because these functions depend on keeping relevant factors in working memory without the confounding influence of non-relevant or distracting information. In PD a lack of dopaminergic activity appears to disrupt the basal ganglia's normal capacity to suppress distracting or inappropriate signals. Thus distracting signals and directives which would ordinarily be suppressed by the basal ganglia are instead

relayed to the pre-frontal cortex and cause difficulty maintaining attention to the salient stimuli or problem (Koziol & Budding, 2009).

Attention deficits can be very disruptive to an individual's day to day functioning (Pernecky et al., 2008). They cause downstream effects on decision making and planning processes that are already inhibited in PD, but also make the completion of complex tasks even more difficult, particularly those that require monitoring over a period of time. In practical terms this may include activities such as cooking or driving. The combination of deficits present in task initiation, motor functioning and attention impact greatly on the capacity of many people with PD to effectively complete their ADLs and to live independently (Pernecky et al., 2008).

3.1.3 *Memory*

PD can reduce an individual's ability to encode and retrieve new memories. Green et al. (2002) determined that memory deficits were present in more than 30% of a sampled PD population and Hannah-Pladdy et al. (2013) reported memory impairments as the most common deficits found in the PD population.

Memory deficits in PD most frequently occurred in the domains of verbal learning and delayed recall. These types of deficits are indicative of problems encoding information correctly. However, unlike individuals who experience Alzheimer's disease, people with PD are able to benefit from probing or semantic cues, suggesting that information may be encoded correctly, but is difficult to access (Emre, 2003a). This is very similar to the differences seen in internally / externally guided behaviours in the population and is consistent with what would be expected in a subcortical pathology. That is, the information is encoded and likely retrieved correctly, but the basal ganglia's inhibited ability to selectively send and block messages to the pre-frontal cortex results in poor

retrieval of the encoded information and associated functional inability to remember the information in everyday life (Koziol & Budding, 2009).

Working memory, too, is affected by the same pathology; the stimulus inhibition deficiency can both prevent erroneous information being supplied to the working memory and can fail to keep required information available to the working memory (Koziol & Budding, 2009). Deficits in working memory further confound the ability for people with PD to solve complex problems by holding information in their mind and manipulating it to produce a result. This can act to further impair the already damaged functions of planning and decision making for individuals with PD.

3.1.4 Language

Language skills allow an individual to communicate through perception and generation of language. Though they are not considered common in PD, some people who experience PD can have deficits in their language abilities. In a similar fashion to memory retrieval deficits, individuals who experience PD can sometimes experience difficulties with language generation due to the deregulation of signal control in the basal ganglia (Koziol & Budding, 2009). This deficit is usually expressed as delayed speech and can inhibit a person with PD's ability to actively participate in conversation in the same way that initiation difficulties in their executive function can inhibit participation in activities (Koziol & Budding, 2009).

Dysarthria can also affect individuals with PD due to the motor components of the disease, but expresses as slurred or unclear speech rather than a difficulty in language production.

3.1.5 *Visuo-Spatial Skills*

Visuo-Spatial skills allow an individual to perceive the details of an object visually, interpret visual cues, and make judgements of depths and distances. Some people with PD have been shown to experience deficits in this area in studies such as Possin, Filoteo, Song & Salmon (2008), who inferred an effect on working memory through difficulty encoding and maintaining information in a PD population. Practically, this may express as difficulty in performing tasks such as visualising a road map to allow the individual to select a series of turns to take to reach a particular destination when driving. However, the study did indicate that spatial and object deficits were distinct within the population, with recall delays detracting from performance on object tasks, but not affecting performance on spatial tasks. This indicates that it is the encoding process which affects spatial tasks, and the recall process which affects object tasks.

3.2 **Aetiology of Decline**

The pattern of cognitive decline in PD is reported differently between research studies. Most studies indicate that deficits in executive function and attention deficits are the earliest to appear, while deficits in visuospatial / constructional skills and memory deficits, particularly free recall, become evident later in disease progression (Kulisevsky & Pagonabarraga, 2009). Stuss and Alexander (2000) propose that executive dysfunction may in fact underpin the dysfunction present in other cognitive domains. Other studies, however, have indicated that executive function deficits are typically found in older people with longer disease durations (Bohnen et al., 2009; Montel & Bungener, 2008).

The rate of cognitive decline in PD can vary considerably. Muslimovic, Schmand, Speelman and de Haan (2007) demonstrated slow decline over the first 2.5 years following diagnosis, however this rate of decline is heavily influenced by a number of external

factors. Hely, Reid, Adena, Halliday and Morris (2008) reported, for instance, that both age and disease duration impact on the rate of decline with older individuals experiencing more rapid decline than their younger counterparts. Conversely, however, Hely et al. report that 19% of individuals with PD develop PD Dementia within 19 years of diagnosis regardless of age of onset.

3.3 Early Cognitive Decline

Cognitive decline in PD is often thought of as affecting only those people with PD who receive a diagnosis of Mild Cognitive Impairment (MCI) or Parkinson's Disease Dementia (PDD). However, individuals with PD who do not meet diagnostic criteria for either of these conditions have been found to experience mild deficits across multiple cognitive domains as part of their disease progression (Hanna-Pladdy et al., 2013). Barone et al. (2011) estimate that these deficits affect 25% of people newly diagnosed with PD.

The progression of impairment seen in early decline in PD is reported contradictorily, similarly to the aetiology of PD Dementia. Some studies have indicated that people in the early stages of PD present with prominent memory impairment (Emre, 2003b), while others have noted the executive function deficits and attention difficulties in the early part of the disease (Lee et al., 2013). In either case, the overall symptomatology of people with early cognitive decline in PD is that they mirror the deficits seen in MCI and PD Dementia, but are of lesser severity (Emre, 2003b).

A likely driver of early cognitive impairment in PD is extra-nigral pathology; i.e. pathology that occurs in areas of the brain outside of the substantia nigra (Hanna-Pladdy et al., 2013). Cortical thinning in fronto-temporal regions in early PD is thought to be responsible for the early executive decline. Hypometabolism of cerebral glucose in temporo-parietal regions is implicated in PD-MCI (Hirano, Shinotoh & Eidelberg, 2011;

Pernecky et al., 2008). While the dopamine depletion that occurs in PD is well documented it is unclear whether cognitive deficits arise from structural deterioration or neurotransmitter depletion (Hanna-Pladdy et al., 2013).

While early cognitive deficits may not be apparent when conducting day to day activities of daily living (ADLs) their accurate and early identification is essential to not only ensure ongoing monitoring of further deficits but to potentially predict those at risk of developing MCI or Parkinson's Disease Dementia (PDD).

3.4 Mild Cognitive Impairment

MCI is a sub-condition diagnosed in people with PD whose ability to function in everyday activities is compromised by poor cognition (Goldman et al., 2012). Though MCI has been diagnosed according to a variety of conditions in the past, the Movement Disorders Society Taskforce has recently codified a set of criteria for the diagnosis, improving the consistency of diagnosis across the PD population (Litvan et al, 2012). MCI is diagnosed on a threshold basis where every day functioning occurs at a level that is considered impaired against a 'normal' level of functioning (Litvan et al, 2012; Mak et al. 2013). Accordingly it may not represent an actual decline but a failure to function at a normal level. For example, a person with PD may have had impaired attention before they were diagnosed with PD which would contribute to a diagnosis of MCI at the time of their PD diagnosis. Conversely, an individual who had had a particularly high level of attention ability before the onset of the condition and who since declined to a normal level of functioning would not receive a diagnosis of MCI. Thus it is important to state for clarity that a diagnosis of MCI in an individual with PD is not necessarily indicative of a decline in function, and a lack of diagnosis is not evidence of a lack of decline in function.

A study by Lee et al. (2013) reports that one fifth of people with PD experience MCI with 19% having quantifiable cognitive deficits upon diagnosis. MCI symptoms are the same as those experienced in early cognitive decline in PD (attention deficits, executive dysfunction, visuospatial and / or memory impairments) but are understood to be more disabling (Emre, 2003b). Typically, a diagnosis of MCI is dependent on a person with PD being defined as impaired on one or more areas of cognitive function (Litvan et al, 2012; Naismith, Mowszowski & Diamond, 2013) without experiencing a level of impairment that would qualify for a diagnosis of Parkinson's Disease Dementia (Litvan et al, 2012; Marras et al., 2013).

A number of studies report MCI as a prodromal state of PDD, with studies demonstrating conversion rates from MCI to PDD at 30% over a 2.5 year period and 60% over a 4 year period, therefore meaning that the early detection of cognitive decline in PD is crucial (Goldman et al., 2012; Lee et al., 2013; Litvan et al., 2012). Of particular importance making arrangements for the future such as granting the Power of Attorney and being prepared for issues around the capacity to make decisions about finances, accommodation and healthcare can be facilitated while the person is still in an able state to contribute to these decisions personally. There is also an important opportunity to provide people with PD, carers and families with education around the likely outcomes of the disease and what it will mean for them in the future. Better understanding of factors that influence disease progression allows more concrete information to be provided and allows the people with PD and their families to be better prepared for the disease progression.

3.5 Parkinson's Disease Dementia

Dementia is the term used to describe the symptoms of several illnesses that affect the brain and cognitive functioning. Dementia is a degenerative process associated with

decline in function across a number of areas and is often indicated by memory loss, confusion, apathy or behavioural changes. Over time, the loss of function associated with dementia can be debilitating.

The most common and most well understood cause of dementia is Alzheimer's Disease (AD) and as such the term "dementia" is often used to characterise the cognitive and functional decline caused by this condition. The neuronal plaques and tangles caused by this disease occur in the cortex of the brain and typically result in focal cortical neurological deficits such as prominent amnesic and word finding problems. In contrast, however, PD affects *sub-cortical* structures (see Chapter 3:) in the brain stem and basal ganglia. People with PD thus do not typically manifest the same set of cortical cognitive deficits. Cognitive decline resulting from sub-cortical pathologies, like PD, is instead characterised by prominent executive dysfunction, memory dysfunction and impaired visuo-spatial skills (Vingerhoets, Verleden, Santens, Miatton & de Rueck, 2003).

Estimation of the incidence of PDD in the PD population varies greatly between studies, ranging between 15% and 70% (Demakis, 2007). While some research attributes this to measurement differences between studies (Demakis, 2007) others postulate that dementia in PD populations may be significantly under-diagnosed and poorly recognised because the executive deficits occurring early in the disease may be less easily recognisable than the prominent memory and word finding deficits associated with cortical pathologies like AD (Marinus et al., 2003).

It should be noted that individuals with PD can experience cognitive impairment without meeting a diagnosis of PDD, with as many as 24% of people who experience PD having some cognitive impairment at the onset of the disease (Stella et al., 2007). This can both contribute to the lack of recognition of PDD in the population and to mask the severity of the condition.

However, individuals who develop PDD require a different approach to those individuals with PD without dementia. PDD is associated with a higher risk of mortality than PD without dementia (Aarsland et al., 2001). People with PDD are also more likely to require nursing home placement and they cause greater care-giver distress than their non-demented counterparts (Aarsland et al., 2001).

3.6 Diagnostic Tools

An important consideration when examining cognitive impairment in PD is the diagnosis of MCI and PDD, not only in terms of classification but also in terms of the strengths and weaknesses of the diagnostic tools used to assess at-risk individuals. Few neuropsychological tools exist solely for the assessment of those with PD. The Mini-Mental Parkinson (MMP), Scales for the Outcomes of PD- Cognition (SCOPA COG), Parkinson Neuropsychometric Dementia Assessment (PANDA) and the PD Cognitive Rating Scale (PD-CRS) are all specific to PD but are brief and often fail to detect some of the subtle deficits associated with PD-MCI (Marras et al., 2013; Reyes et al., 2009). Reyes et al. (2009) indicate that SCOPA-COG, in particular, is sensitive to only a limited set of cognitive functions that are impaired in PD.

To effectively identify PDD, a range of tests across all cognitive domains needs to be administered examining executive function, memory, attention, information processing speed, visuospatial constructional and language abilities (Dubois et al., 2007). While these fuller neuropsychological assessments offer a more accurate picture of the individual's cognitive functioning, they are often deemed inappropriate in clinical practice due to the lengthier time they take to administer; the cost of administration and the relatively low value they are currently perceived to add to management, treatment and outcomes for the person with PD (Dubois et al., 2007). Many neuropsychological assessment tools can also

be affected by the motor components of the disease which can lead to over reporting of impairment in some areas due to difficulties in completing physical tasks (Dubois et al., 2007).

Anti-Parkinsonian medications have also been recognised as having some effect on cognitive performance (Schoenberg et al., 2012). As the severity of motor symptoms increase, the amount of medication required increases. Hence there may be some increased impact on cognition due to medication with increase in age. However, the impact of increased motor symptoms without medication is more likely to affect cognitive test performance than the impact of the medication itself, making this a difficult area to control for in research.

The high correlation between PDD and quality of life, level of motor impairment and levodopa dosage emphasises the importance of accurate diagnosis of these cognitive aspects of the disease (Hanna-Pladdy et al., 2013). Similarly, the effects of MCI and even the mild cognitive deficits associated with early decline can have a significant impact on an individual's function, and better understanding of these could lead to improvement in treatments and outcomes for people with PD.

Chapter 4: Mood and Cognition

Due to the high prevalence of common mood disorders and the potential that they have for cognitive side effects it is imperative to examine the impact both anxiety and depression have on people with Parkinson's Disease (PD). Anxiety and depression are both commonly associated with PD, with a higher incidence of both reported among people with PD than in the general population (Rodriguez-Blasquez, Frades-Payo, Forjaz, de Pedro-Cuesta & Martinez-Martin, 2009). Depression is one of the most common psychiatric disturbances experienced by people with PD with research estimating that up to 50% will meet criteria for clinical depression at some stage throughout their disease duration (Ravina et al., 2007). While the majority of these people will have mild clinical depression around 17% will meet criteria for major depressive disorder necessitating ongoing treatment with therapy, anti-depressant medication and in some cases electro-convulsant therapy (ECT) (Ferreri, Agbokou & Gauthier, 2006; Reijnders et al., 2008). Anxiety is present in around 40% of people with PD, and has been shown to be present before the onset of motor symptoms in some cases (Ceravola et al., 2010).

Mood is also an important factor to consider in clinical practice, especially when considering the potential presence of a dementing process, with clinical guidelines recommending the identification and subsequent treatment of mood disorders prior to the diagnosis of a subcortical degenerative process (Ceravola et al., 2010). The cognitive effects of depression are well documented with memory, attention and slowed processing speed all being identified as potentially affected by persistent low mood. This can also affect performance on other cognitive measures, including the National Adult Reading Test (Watt & O'Carroll, 2009). Ceravola et al. (2010) determined that people with PD who met criteria for depression and remained untreated for it demonstrated increased disability and a higher need for treatment for PD symptoms.

Despite this, research suggests that depression is both under-identified and under-treated in the PD population, with one research study finding that two thirds of people with PD who met criteria for clinical depression were not previously diagnosed and hence not receiving any treatment for their psychiatric mood disturbance (Ceravola et al., 2010; Ravina et al., 2007). Ravina et al. (2007) found that most individuals who receive pharmacotherapy for depression have moderate to severe presentations.

4.1 Depressive Symptoms in people with PD

The under-diagnosis of depression is, at least in part, attributable to the high overlap that depressive symptoms have with PD with symptoms; fatigue, insomnia, sleep disturbances, restlessness, psycho motor slowing and retardation, reduced mimics, reduced sex drive and apathy are regularly identified as manifestations of PD rather than depression itself (Lemke et al., 2004; Ravina et al., 2007; Rodriguez-Blazquez et al., 2009). Such is the intertwining of the conditions that in 2006 a recommendation was made by NINDS/NIMH to include depression as a diagnostic criterion for PD in the DSM (Marsh et al., 2005).

Research suggests that those individuals who experience depressive symptoms as a result of PD have a tendency to have a different constellation of symptoms compared to those individuals solely with primary depression. Richards (cited in Ferreri et al., 2006) cites that those with PD experience more anxiety, pessimism, suicidal ideation, cognitive deficits, irritability and ruminations whereas purely psychiatric populations experience more early morning awakening, pervasive low mood and pessimistic thoughts about not only themselves but the world and their future as well. Major depressive disorder has also been identified as a risk factor increasing the likelihood of the development of PD Dementia (Ceravola et al., 2010).

Depression in PD can act both to exacerbate symptoms and to reduce the effectiveness of disease treatments (Uekermann et al., 2003). Depressive symptomatology impacts on the individual's ability to conduct activities of daily living and, by doing so, reduces an already impaired quality of life independent of any effects from the motor symptoms of the disease (Leentjens et al., 2012; Lemke et al., 2004). Depressed people with PD are up to 83% more likely to be judged as needing symptomatic therapy for PD compared to non-depressed subjects (Ravina et al., 2007). This indicates that the treatment of depression symptoms may help people with PD to better manage their other symptoms, and hence highlights the importance of treating the depression that occurs in PD.

4.2 Symptoms of Anxiety in PD

While depression and anxiety have a high overlap in symptoms distinct anxiety syndromes can be seen within the PD population. Leentjens (2008) found that up to 30% of PD patients experience panic disorder while 11% meet the criteria for Generalised Anxiety Disorder. Hanna and Cronin-Golomb (2011) suggests that these anxiety symptoms have even more detrimental effects than depression on the PD population. Anxiety in people with PD is often cyclic; anxiety can lead to an increased perception of motor symptoms, more severe gait problems, dyskinesias, freezing, on/off fluctuations (Leentjens, 2008), and these symptoms can then lead to increased anxiety.

The most common anxiety symptoms in PD are panic attacks, particularly in off states, Generalised Anxiety Disorder (GAD) and social phobias (Ceravola et al., 2010). Panic Disorder is observed in as many as 19% of those with PD. Ceravola et al. (2010) also postulates that the autonomic dysfunction that typically accompanies PD that causes

symptoms such as fluctuations in heart rate and blood pressure may play an underlying role in the development and maintenance of anxiety disorders.

4.3 Diagnosis of Mood Disorders in PD

The overlap in symptoms between PD and common mood disorders means that accurate diagnosis of anxiety or depression in the population is fraught with difficulty. Most quantitative depression measures such as the Beck Depression Inventory (BDI), Geriatric Depression Scale (GDS) and the Hamilton Depression Scale (HAM-D) include questions that examine psychomotor agitation which can spuriously increase the rate of those who are identified as experiencing depression on these measures (Rodriguez-Blasquez et al., 2009). Conversely, this symptom could also be hidden by the bradykinesia that is often present in people with PD (Ceravola et al., 2010). Similarly anxiety is often under diagnosed because of symptom overlap with autonomic symptoms such as fatigue, cognitive difficulties and sleep disturbances. For clinical and research purposes it is important utilise methods that are able to accurately identify mood disturbance in the PD population.

While impractical for many research studies, due to funding and time constraints, research suggests that the most accurate identification of mood disturbance is completed via the use of quantitative questionnaires in combination with structured psychiatric interviews such as the Structured Clinical Interview for Diagnostics (SCID) (Lemke et al., 2004). In the absence of time and funding to use these best practice measures, many clinicians currently rely on subjective reports of feelings of emptiness, hopelessness and anhedonia to make a diagnosis (Lemke et al., 2004).

The Hospital Anxiety and Depression Scale (HADS) has been identified as an effective screening tool in PD as it omits many of the somatic symptoms that can occur in

PD (Muslimovic, Post, Speelman & Schmand, 2005; Rodriguez-Blasquez et al., 2009). The HADS is a 14 item questionnaire that asks participants to rate the regularity of feelings that they have experienced that pertain to mood disorders and provides a separate rating for levels of anxiety and depression. The HADS is a relatively inexpensive and brief assessment that has been demonstrated to be both reliable and valid in PD populations (Rodriguez-Blasquez et al., 2009). The research application of the HADS, particularly in populations where motor symptoms are present, is an area of interest for further research.

4.4 Origins of Mood Disorders

A somewhat contentious issue throughout the literature on mood and PD is whether or not the mood disturbances that exist in PD are exogenous or endogenous in nature and a wealth of literature exists supporting both notions. Organic theories of depression in PD postulate that the dysregulation of neurotransmitters dopamine, serotonin and norepinephrine plays a major role in the occurrence of depression (Ferreri et al., 2006). It is thought that this change in neurotransmitter function may also be the reason that psychiatric symptoms are often better while the person is an 'off' state (Lemke et al., 2004). Autopsy studies reveal that depressed people with PD present with degeneration of the nucleus ceruleus- the major brain centre for noreadrenaline (Lemke et al., 2004). Additional evidence for endogenous depression is the fact that it's found to be highly treatable with pharmacotherapy such as selective serotonin re-uptake inhibitors, serotonin norepinephrine reuptake inhibitors and tricyclic antidepressants (Lemke et al., 2004). However, while the anticholinergic effects of antidepressants may have the additional benefit of improving motor symptoms they can worsen cognitive symptoms so need to be used with caution.

Some research suggests that depression can be exogenous or reactive in nature. This is understandable given the unpredictability of symptoms, degenerative nature of the disease and general difficulty in coping with a loss of independence over time (Leentjens et al., 2013). Whether it is exogenous or endogenous, the correct identification and treatment of depression is important from a disease management perspective with depression being found to lead to poorer long term outcomes with faster disease progression of physical symptoms as well as greater cognitive decline, caregiver distress and decreased quality of life and medication compliance being found in those with depression and PD (Menza et al., 2009).

4.5 Psychiatric Disorders in PD

In addition to cognitive decline and dementia, people with PD can sometimes experience psychosis as a part of their disease progression. Psychiatric delusions, usually accompanied with hallucinations, are reported in up to 10% of people with PD (Ceravola et al., 2010). Delusions present typically involve aspects of jealousy, persecution or abandonment (Ceravola et al., 2010).

It is thought that the hallucinations experienced by people with PD are likely the result of the formation of Lewy bodies (Ceravola et al., 2010). Alternatively, prolonged use and high dosages of anti-Parkinsonian medications can result in hallucinations. The particular medications are dopamine agonists, and prolonged use and/or high dosages can result in over-stimulation of the D3 and D4 dopamine receptors (Ceravola et al., 2010). This risk is particularly relevant to individuals with early onset PD as they would typically use anti-Parkinsonian medication for a longer period of their life. In addition, this also means that those who are first diagnosed are susceptible to psychotic type symptoms while their medication is titrated and a suitable dosage is ascertained.

Those with PD who experience psychosis demonstrate faster disease progression and a worse prognosis both in terms of higher mortality rates and a greater need of placement in residential aged care facilities (Ceravola et al., 2010). Therefore the risk of development of psychosis needs to be taken into account in devising treatment plans for people with PD, particularly in terms of the use of dopamine agonists to treat Parkinsonian symptoms. Nevertheless, the relatively low incidence of psychiatric disorders in the population as well as limitations on time and participant pool means that psychiatric disorders in PD were not considered as part of this research.

Chapter 5: Cognitive Reserve Theories

An area that is currently of interest in neurological literature is the notion of cognitive reserve. According to this theory some individuals have pre-morbid neurological, cognitive and lifestyle factors that are protective against cognitive decline, despite the presence of brain pathology. This notion has primarily been investigated in cortical dementias, and AD most clearly. There are differences, however, between cortical and sub-cortical brain pathologies and it appears important to examine the notion of cognitive reserve in sub-cortical diseases such as PD. The possibility that some people with PD may be more or less protected from associated cognitive decline by pre-morbid brain and lifestyle factors is a central question of the current research.

5.1 Reserve Theories

Reserve theories attempt to explain findings that the amount of neurological damage to a brain and the cognitive impairment associated with it do not follow a consistent relationship; that is, two individuals who experience similar amounts of damage to their brain, through trauma or disease, can have very different levels of cognitive deficits, even if these deficits are in the same function(s). The theory of reserve, then, is that there exists some factor in the individual's brain that protects them against cognitive deficits as a result of damage (Stern, 2002). Reserve theories exist in both active and passive forms.

5.2 Passive: Brain Reserve

Brain reserve is a passive theory of reserve which posits that those individuals with physically larger brains, more neurons or more synapses, can sustain more damage than those with smaller brains, fewer neurons or fewer synapses, without experiencing the same amount of cognitive deficit (Barnett, Salmond, Jones & Sahakian, 2006). In simple terms, the basis of this theory is that if there is more brain to begin with, the individual can sustain more damage and still retain enough neurons and synapses to function in a relatively unimpaired fashion.

Brain reserve has been measured in a variety of ways depending on the equipment and funding available to the study. Katzman (1988 in Valenzuela, 2008) found that individuals with more large pyramidal neurons retained better cognitive functions than their counterparts throughout dementia. This aspect, however, is difficult to measure, and hence other measures of brain reserve have been utilised including head circumference, head girth, and intra-cranial volume (ICV). These measures have typically not demonstrated a relationship across the entire spectrum, but rather indicate an increase in impairment caused by dementia at the low end of the scale.

A study by Mortimer, Snowden and Markesbery (2003) investigated a population of nuns using head circumference as a measure of brain reserve. While their results indicated that there was a relationship between the head circumference and dementia, again at the lower end of the scale, they indicated that head circumference has only a moderate correlation with ICV, and they believed a more accurate measure of ICV, such as MRI (Magnetic Resonance Imaging) or CT (Computerised Tomography), would demonstrate a stronger relationship.

5.3 Active: Cognitive Reserve

“Cognitive reserve” is an active theory of reserve based on brain compensation for tissue lost to disease. In this model, functions originally performed by parts of the brain now diseased are instead performed by non-diseased tissue capable of taking over the role (Sachdev & Valenzuela, 2009). Cognitive reserve, then, is a measure of the efficiency of the brain. A highly efficient brain will perform more functions with a similar number of neurons than a less efficient brain (i.e. one with less cognitive reserve). It follows, then, that in two brains experiencing similar amounts of damage the more efficient brain would be able to perform more cognitive functions within the remaining undamaged neurons and synapses and hence the individual with greater cognitive reserve experiences less cognitive deficit as a result of the damage. The protective nature of cognitive efficiency has been demonstrated to be relevant to dementia populations across a number of studies that have been collated and reviewed by Valenzuela and Sachdev (2006b) to demonstrate a large overall effect for cognitive reserve helping to delay or prevent cognitive decline.

Cognitive reserve can be measured in a number of ways. Valenzuela (2008) proposes three types of measurement as being of interest in determining cognitive reserve; pre-morbid IQ, cognitive efficiency, and behavioural or environmental measures. Other studies have also identified education level as a valuable measure of cognitive reserve (Jones et al., 2011).

5.3.1 *Pre-Morbid IQ*

Pre-morbid IQ is an estimate of overall cognitive functioning before the effects of a disease, brain injury or a dementing process. Several studies have indicated that pre-morbid IQ can be the most powerful measure, where individuals with a higher IQ have a greater cognitive reserve than their counterparts (Albert & Teresi, 1999).

This extends to the PD population, where a study by Koerts, L. Tucha, Lange and O. Tucha (2013) identified pre-morbid IQ as a delineator of cognitive reserve by examining comparative incidence of MCI for different IQ groups. Pre-morbid IQ can be estimated from an individual's level of education, or via a specific measure such as the National Adult Reading Test (NART).

The NART asks participants to pronounce a list of words of increasingly difficult pronunciation and counts the errors made. The test is structured such that the words cannot be pronounced correctly phonetically and hence the participant must demonstrate existing knowledge of the word's pronunciation in order to pronounce it correctly. The error score is then converted to an overall IQ score based on a standardised score conversion. The NART addresses a domain of crystallised intelligence that is thought to be relatively well protected from the effects of brain injuries, be they obtained by accident or disease. By measuring this area of intelligence, then, the NART gives an indication of the level of intelligence of the individual before their accident or the onset of their disease; a pre-morbid IQ. The NART is a valuable measure as it is administered quickly and does not require physical input from the participant, something that is often affected in acquired brain injuries (Nelson & Willison, 1991). The reliability and validity of the NART have been assessed by a number of studies through comparison with other measures of IQ, including the WAIS, and have demonstrated strong correlations between the two measures (Nelson & Willison, 1991).

Richards and Sacker (2003) indicated that the NART is an effective measure of pre-morbid IQ and is therefore an appropriate measure to use in studies investigating the influence it as a factor. The NART has been validated in dementia populations and demonstrated to be valid for use in the populations (McGurn et al., 2004 in Starr & Lonie, 2008).

5.3.2 *Cognitive Efficiency*

Cognitive efficiency is a measure of the lateral thinking capabilities of the brain; that is, a brain with higher cognitive efficiency is practiced in approaching and solving the same or similar problems in a variety of different ways. The implication of this, then, is that the more cognitively efficient brain has greater plasticity and is able to approach similar problems through a number of methods or pathways (Stern et al., 2003). While this is an important aspect of measuring reserve, it is not a practical measure to use in a research or clinical situation; there is no standard method for quantifying the cognitive efficiency of an individual and hence proxy measures are used instead (Stern, 2002).

As can be demonstrated in (Stern, 2012) much evidence exists for brain training to ward off neurological diseases such as Alzheimer's Disease with studies finding that those who participate in brain training exercises not only warding off the development and progression of disease but enhancing their cognitive ability as well.

5.3.3 *Lifestyle Factors*

Behavioural and environmental factors that have implications in the development of dementia have been identified in a number of studies including Qui, de Ronchi and Fratiglioni (2007) who identified factors such as education, social networks, physical activity and mentally stimulating leisure activities as preventative in the development of dementia. These same factors have been identified by Stern (2003) and Valenzuela (2008). If these factors are protective against dementia it follows that they may be considered indicators of an individual's cognitive reserve.

5.3.4 *Physical Activity*

The role of physical activity in maintaining good health, both from a physical and mental perspective is well established (Stern, 2012). Balsamo et al. (2013) found that physical exercise acts as a protective mechanism against cognitive decline in older individuals. However this study examined current exercise as a means of delaying further decline in individuals already diagnosis with a cognitive impairment and did not look at the effects of exercise earlier in life as a means of building up reserve. Dik, Deeg, Visser and Jonker (2003) investigated the effects of participation in physical activities earlier in life and found evidence that this participation helped to retain processing speed in older individuals, but not overall cognition. However, Dik et al. did suggest that their findings were evidence to support the theory of physical activity developing cognitive reserve in the Alzheimer's Disease population.

While participation in physical activities appears to have some treatment benefits at any stage of life, the motor symptoms present in a population such as those with PD or simply the effects of the aging process may limit the efficacy of exercise as a therapeutic aid against disease progression.

Research into the effects of exercise has focussed on prevention of disease progression in cortical dementias. Hence it is an area which still needs to be explored in populations that experience sub cortical dementias such as PD.

5.3.5 *Leisure Activities*

Involvement in mentally stimulating leisure activities has been demonstrated to have a positive effect on cognition (Mitchell et al., 2012). A review article by Valenzuela and Sachdev (2006a) highlighted the importance of considering involvement in mentally stimulating leisure activities in the cognitive process of dementias. Mentally stimulating

leisure activities is a broad umbrella that can refer to a large number of activities. For the purposes of research, a subset of these factors has been selected, both for their measurability and their commonality; while it may be mentally stimulating to attempt to learn pi to 100 decimal places there are few individuals in the population to give this statistical power. Mentally stimulating activities that are of interest to research, then, include speaking a second language, playing a musical instrument, artistic pursuits, reading and travel. Similarly to physical activity, participation in mentally stimulating leisure activities has been demonstrated to have positive effects in the Alzheimer's Disease population. Scarmeas and Stern (2003) reviewed a number of studies in this area highlighting reduced incidence of dementia for those involved in complex mental leisure activities and higher survival rates among dementia patients with high involvement in leisure activities.

5.3.6 Musical Activities

Hanna-Pladdy and MacKay (2011) demonstrated that older individuals who had spent a significant amount of time in their lives playing musical instruments had preserved brain function, particularly in the areas of memory, naming and executive functions. Zatorre, Chen and Penhune (2007) highlighted the fact that the basal ganglia are involved in movement timing, a critical component in playing an instrument, and that people with PD have been shown to have impairment in this area. Further research by Hanna-Pladdy and Gajewski (2012) has highlighted this area as important for future studies into brain training and cognitive reserve.

5.3.7 Bilingualism

Antoniou, Gunasekera and Wong (2013) postulated that speaking a second language enhances cognitive reserve by utilising a number of cognitive processes such as

inductive reasoning, sound discrimination, working memory, task switching, rule learning and semantic memory activating multiple brain networks predominately in the frontal and temporal lobes. Recent neuro-imaging studies have demonstrated that those who are bilinguals can withstand more neurodegenerative change than monolinguals of similar intellectual capacity (Schweizer, Ware, Fischer, Craik & Bialystok, 2012).

However, speaking a second language may be as much a measure of the passive model brain reserve as of the active model cognitive reserve. Luk, Bialystok, Craik and Grady (2011) used diffusion tensor imaging to demonstrate that those who are bilingual have greater connectivity between their corpus callosum and frontal lobes suggesting that speaking a second language may increase inter-neuronal connectivity hence act as a mechanism for brain reserve. The study demonstrated that those with individuals who are bilingual are more likely to maintain white matter integrity compared to their monolingual counterparts (Luk et al., 2011).

By whichever of these mechanisms it occurs, there is evidence to suggest that speaking a second language has an effect on the decline associated with dementia. Recent research demonstrates that while lifelong bilinguals can develop symptoms of Alzheimer's Disease they tend to do so at an older age than their monolingual counterparts (Gold, Johnson & Powell, 2013).

While these effects have been found to exist in cortical conditions such as Alzheimer's Disease they are yet to be studied in sub cortical disease states such as PD. However, it has been shown that bilinguals typically have better control over their executive functioning, which is thought to stem from practice at task switching (Bialystok, 2011; Gold et al., 2013). Given that executive functioning is one of the areas most affected by subcortical dementias this makes speaking a second language an area of interest in this population.

5.3.8 *The Lifetime of Experiences Questionnaire*

Valenzuela and Sachdev (2007) consolidated these social, physical and mentally stimulating leisure activity factors into the Lifetime of Experiences Questionnaire (LEQ) allowing a quantitative measure of these factors which, in turn, could be used as a measure of cognitive reserve. The LEQ provides a measure of different types of life experiences across three stages of life; young adult, adult, older adult. At each stage of life individuals are asked to rate the frequency of their level of involvement in a number of life activities, including playing musical instruments, involvement in clubs and charities, level of physical activities and speaking multiple languages. The LEQ then addresses a score to each type of activity to provide a quantitative level of involvement in each type of activity at each stage of life. These scores can be used to measure these levels of involvement, by section, life stage or overall, as a research tool to check whether or not relationships exist between levels of such activities and other outcomes.

In the case of cognitive reserve, analysis against LEQ scores allows a number of questions to be addressed. It has already been discussed that research has identified the types of activities measured by the LEQ as being associated with cognitive reserve (Stern, 2003; Valenzuela, 2008). However, this quantitative measure allows further investigation into the efficacy of particular types of activity at particular stages of life in preventing cognitive decline. In terms of clinical interest, the life stages of the questionnaire provide the opportunity to identify particular activity types that may help to slow decline after diagnosis, and hence these activities could be included in treatment plans for people with PD to help reduce the cognitive impact of their disease.

Valenzuela (2008) has shown that a relationship exists between LEQ scores and cognitive decline in Alzheimer's Disease dementia populations. However, there remains a need for further research to properly establish the LEQ as a valid measure of cognitive

reserve in Alzheimer's Disease and to investigate whether this can extend to other populations such as those with subcortical dementias. It is important, then, to further investigate the role of the LEQ in measuring cognitive reserve as successful proving of such would allow deeper investigation of the potential links and treatment outcomes to be justified, potentially across multiple neurodegenerative conditions.

One potential issue with the LEQ as a measure of involvement in activities across life stages is the self-report structure of the questionnaire. Studies have demonstrated that over reporting of participation can occur in self-report format, particularly when the activity is regarded as socially desirable (Adams et al., 2005). This has been shown to relate directly to physical exercise, which is one of the activities measured on the LEQ (Rzewnicki, Auweele & De Bourdeaudhuij, 2003).

5.3.9 Education

Education is another measure that has traditionally been associated with cognitive reserve (Valenzuela & Sachdev, 2006b). Education, as a measure, refers to the level of formal education that an individual has received during their lifetime. Typically, education is referred to by the highest year of schooling completed by the individual, with tertiary and post graduate education considered higher again than college level; it does not take into account the quality of the education received. Jones et al. (2011) identified education level as the most widely used measure of cognitive reserve across all diseases and both Armstrong et al. (2012) identified education as a valid measure of cognitive reserve in the PD population. Wilson, Barnes and Bennett (2003), however, determined that education level was only responsible for 6% of the variation in cognitive activity, another measure of cognitive reserve. Furthermore, Pai and Chan (2001) investigated the effects of education on cognitive performance in the PD population and found that individuals experienced

more decline than those with lower education. This result was attributed to more educated individuals being more sensitive to decline, but it does raise doubt about the validity of education as a measure of cognitive reserve in the PD population. One impediment to using education as a measure of cognitive reserve in a study involving PD is the lack of educational opportunities that were available to participants who are of an age to participate in the research.

5.4 Threshold / Linear Modelling

In both active and passive theories of reserve, there are two schools of thought as to the manner in which reserve protects against dementia. One of these is that there is a linear protective relationship between reserve and cognitive decline; i.e. higher levels of reserve are associated with lower levels of impairment. The second manner is a threshold model which, rather than suggesting that the protection offered by reserve is theoretically infinite, there exists a level of reserve above which an individual does not experience impairing deficits.

This threshold model is particularly evident in studies measuring brain reserve; typically these studies have demonstrated that there is a relationship at the lower end of the scale, but one which is not so demonstrable at the higher end of the scale (Valenzuela, 2008). However, Mortimer, Snowdon and Markesbery (2003) discovered a similar phenomenon when measuring decline against education level, a factor that has been used to measure cognitive reserve both from a behavioural perspective and as an indicator of pre-morbid IQ.

5.5 Cognitive Reserve in Parkinson's Disease

The question of whether pre-morbid IQ, education and lifestyle factors appear to moderate the cognitive effects of PD is central to the current research. There are a very limited number of studies that have investigated cognitive reserve in PD directly, and only two that have demonstrated a positive effect for reserve in the PD population. Koerts et al. (2012) demonstrated a positive protective effect for pre-morbid IQ in PD by measuring the instance of cognitive impairment against pre-morbid IQ in a PD population. Armstrong et al. (2010) demonstrated a protective relationship with education, often regarded as a proxy for pre-morbid IQ, using a similar methodology. However a study by Pai and Chan (2001) had demonstrated the reverse effect for education, demonstrating a higher level of decline among those who had attained higher levels of education. The influence of lifestyle factors on cognitive reserve in the PD population has not previously been studied, except for the inclusion of PD in more generalised dementia populations. Given the limited body of research, and the conflicting nature of the results, it is clear that the role of cognitive reserve in PD remains poorly understood.

Chapter 6: Study One - Cognitive Reserve in Parkinson's Disease

6.1 Aim and Hypotheses

Much research into cortical dementias (notably AD) has supported the idea that people high in “cognitive reserve” (indexed usually as premorbid IQ or education) may experience less cognitive decline than people with lower “cognitive reserve”, despite similar levels of actual brain pathology. Very little research exists on the cognitive reserve hypothesis in sub-cortical dementias. The current study sought to examine whether premorbid IQ and education are predictors of cognitive decline in a Parkinson's Disease population. Just three previous studies appear to address this issue with two finding a positive relationship between IQ or Education (Armstrong et al., 2010; Koerts et al., 2013) and one study finding an inverse relationship between education and cognitive decline (Pai & Chan, 2001). Identifying factors that predict the amount of decline experienced by people with PD is important in providing treatment regimes suited to the individual.

Based on the reviewed research the following were hypothesised:

1. Pre-morbid IQ will be negatively correlated with cognitive decline in Parkinson's Disease.
2. Education level will be negatively correlated with cognitive decline in Parkinson's Disease.
3. Education level will correlate highly with pre-morbid IQ.
4. Pre-morbid IQ and education will be associated with performance in cognitive domains affected by Parkinson's Disease but not with

performance in cognitive domains less commonly affected by Parkinson's Disease. Specifically, pre-morbid IQ and education will be associated with performance on measures of executive function and attention, but not with performance on measures of visuo-spatial and language functions.

5. Standardised scores on subtests will demonstrate a relationship with pre-morbid IQ indicating that functional starting point has an effect on functional end point.

6.2 Methodology

6.2.1 Participants

A sample of 88 participants was obtained from both geriatric and neurological outpatient clinics at the Royal Hobart Hospital, the tertiary treatment centre for public patients with Parkinson's Disease. Ethical approval to access patients from these clinics was obtained from The Tasmanian Health and Medical Research Ethics Committee (approval number: H10104).

Participants were selected on the basis that they had a diagnosis of Idiopathic Parkinson's disease, regardless of disease duration, medication and disease state. Patients with concomitant neural problems, such as stroke or multiple sclerosis, were excluded. The sample consisted of 52 males and 36 females representative of the population sample.

For statistical analyses years of education, disease duration, whether or not the individual was taking dopaminergic agents and sex were also obtained.

6.2.2 Selection of Measures

In order to determine whether or not a factor is predictive in prevention of cognitive change we must first determine a method by which to measure an individual's level of cognitive functioning and the change in their functioning over time. Though there are several well established instruments that are used for the measurement of cognitive function, selecting one that is appropriate for use in a study involving a population of individuals with Parkinson's Disease is not straightforward. Consideration must be given to determine an instrument that is minimally affected by the motor component of the disease to allow accurate measurement of the individual's functioning. Conversely, the instrument must assess the cognitive domains that are affected by the disease's progression in order

to demonstrate the individual's decline accurately. Though the timeframe of this study did not allow for a longitudinal design, it is advantageous to consider measures that can be readministered after a time period in order to provide comparisons of cognitive function.

Additionally, in order to determine cognitive decline a baseline measure must be established. It is not within the limitations of this research to conduct multiple interviews with participants, hence there is a need to utilise a separate measure to determine baseline functioning as a point of comparison. This measure too must meet the above requirements of being appropriate to the population, but with the proviso that it cannot be affected by those aspects of cognitive function that are influenced by the progression of Parkinson's Disease.

The combination of these two requirements means that decline must be determined by comparison of a more general level of functioning estimated through two different approaches; one that is influenced by disease progression to give a contemporary level of functioning, and one that is not to provide a baseline for comparison.

Affected Cognitive Domains

The cognitive domains that are affected by the progression of Parkinson's Disease are discussed in detail in chapter 2. However, for the purpose of completeness it is worthwhile to briefly recap them here. Individuals who experience decline as the result of a sub cortical dementia such as Parkinson's Disease typically experience reduction in ability in executive functions (related to goal directed activities and planning) and attention (staying oriented to tasks). Memory deficits are also present in many individuals with Parkinson's Disease, though these are less consistent and measurement may be affected by attention deficits.

To align with the requirements outlined above, then, it is necessary to determine a measure of cognitive function that assesses attention and/or executive domains, with measurement of memory also advantageous, to give a rating to current cognitive function. Conversely, a measure that is unaffected by any of these domains, executive function, attention or memory, must also be determined to provide a baseline level of functioning.

Intelligence Quotient

The most commonly used measure of an individual's cognitive function is Intelligence Quotient or IQ. IQ is generally thought of as an aggregation of a number of sub domains of cognitive functioning which allows for it to be estimated in a number of ways to give an overall estimate of functioning.

IQ is a useful measurement because of its commonality amongst instruments, that is, there are several measures that approximate IQ in different ways. Similarly, many of the available instruments measure IQ on the same scale, with a standardised mean and standard deviation, which allows simple comparison of scores without the need for complex algorithms to convert between the outcomes of one measure and another. Because these measures are normalised against a standard distribution this means that placement of an individual within the curve, via their instrument score, should have the same meaning for each instrument. This allows direct comparison between the measures in a way that can be easily interpreted.

For example, the Wechsler Adult Intelligence Scale (WAIS) and the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) both measure IQ with a mean of 100 and a standard deviation of 15. Because both are measuring the same underlying construct on the same scale it is expected that an individual would score the same or similar on each measure. This has been demonstrated, and is in fact part of the

basis of the validity assessment of the RBANS. While the WAIS can have learning effects when given to the same individual multiple times, the RBANS has multiple forms to make it suitable for longitudinal studies. In a case where a baseline IQ assessment was performed using the WAIS, change in cognition at a later time could not be assessed by repeating the same measure because of the learning effects present in the instrument. However, because the RBANS measures the same construct and uses the same output scale, the outcomes of the RBANS taken at a later time could be compared to the baseline WAIS score to give a measurement of change of function.

While all of the above points make IQ useful as a scale for comparison, it also introduces incorrect assumptions of similarity. Consideration must be given to whether the measures selected for comparison are genuinely assessing the same underlying ability or are simply measuring different constructs.

Measures of Cognition

Wechsler Adult Intelligence Scale

The most well established measure of IQ is the Wechsler Adult Intelligence Scale (WAIS), currently in its fourth revision. The WAIS gives a measurement of intelligence based on an aggregation of four index scores which are, in turn, aggregations of subtest scores that are relevant to that cognitive domain. The sub domains measured by the WAIS are Verbal Comprehension, Working Memory, Perceptual Organisation and Processing Speed. The WAIS IQ score is normalised around a mean of 100 and a standard deviation of 15.

While the WAIS is a well-established measure it has some features that make it less than ideal for research in a Parkinson's Disease based population. For one, it is slow to administer with a single assessment taking approximately two hours to complete.

Secondly, there are a number of subtests of the WAIS, including block design and coding, which are both time based and require motor skills from the participant. Including these tests in assessment would adversely affect the cognitive scores of participants with Parkinson's Disease based on their physical disability rather than any representation of their cognitive abilities.

Repeatable Battery for Assessment of Neuropsychological Status

The Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) is another measure that produces an estimate of IQ by combination of sub domain scores. The domains measured by the RBANS are Immediate Memory, Visuospatial / Constructional, Attention, Language and Delayed Memory. Similarly to the WAIS, the RBANS produces a measure of IQ that is normalised around a mean of 100 and a standard deviation of 15.

The RBANS has several advantages over the WAIS for use in a Parkinson's Disease based population. It takes around 30 minutes to administer, which is more useful in research than the two hours taken to administer the WAIS. Attention is measured as its own sub domain, which provides a measure of interest in Parkinson's Disease where attention is one of the domains affected by disease progression. It also separates memory into two sub domains, Immediate Memory and Delayed Memory, which are also of interest in Parkinson's Disease progression. Like the WAIS, however, it does not directly measure any aspects of executive function. The RBANS has three subtests that require motor components, Coding, Figure Copy and Figure Recall. Of these, only coding is timed and hence is the only task that should be adversely affected by the motor component of Parkinson's Disease. This may lead to a reduction in attention scores across the sample. The Figure Copy and Figure Recall tests require the drawing of a complicated figure, which requires a motor component, however the scoring of these tests is around the placement,

size and relationships of the various figure components and hence is relatively unaffected by deficiencies in motor skills.

The RBANS has been validated against the WAIS in research and has been shown to have strong reliability and construct validity. Results between the WAIS and the RBANS are highly correlated indicating that they are measuring the same underlying construct. That is, an individual who is assessed on each measure would be expected to produce the same result on each measure. Yang, Garrett-Meyer, Schneider, Gollomp and Tilley (2009) have raised questions about the reliability and sensitivity of the RBANS in detecting deficits in early dementia populations, but other studies, such as Morgan, Linck, Scott, Adams and Mold (2010) have demonstrate distinction of measurement on the same indexes. While there is some division in the research, there is evidence available to support the use of the RBANS in the PD population.

The RBANS has an additional utility in research because it is repeatable. The questionnaire has multiple forms which mean that it can be administered on multiple occasions without the risk of learning effects. This makes the RBANS a useful tool for longitudinal studies that need to measure cognitive functioning at multiple time points, and in doing so, measure cognitive change.

Beatty et al. (2003) highlighted the use of the RBANS in dementia populations, and specifically in PD. The authors indicated that because of its strong reliability, well researched normative data, and comparatively short administration time the RBANS is a valuable measure in this population.

The Digit Span subtest of the RBANS differs from the Digit Span subtest of the WAIS in that it includes on less aspect of testing by comparison. Both tests require the participant to remember lists of numbers of growing length and repeat them to the

interviewer verbally in the order that they were given. Each test has the same patterns of sequence length, the same failure conditions, and the same scoring. However, the WAIS Digit Span test has an additional section where the participant is asked to repeat the numbers in the reverse order than they were supplied in. This allows some extra information to be gathered from the WAIS Digit Span test than is gathered from the RBANS test. This information is useful in a Parkinson's Disease population.

National Adult Reading Test

The National Adult Reading Test (NART) measures IQ differently to the other tests described. The NART provides an estimate of pre-morbid intelligence, i.e. intelligence before injury or disease occurred. This measure is provided through utilisation of a test that assesses crystallised intelligence. Specifically, the test requires participants to read aloud a list of words of varying degree of obscurity and the number of errors in pronunciation are recorded by the assessor. The number of errors is then checked against a scale to provide an estimate of the individual's IQ. The NART uses the same scale as both the WAIS and the RBANS for measurement of IQ, normalised around a mean of 100 with a standard deviation of 15.

The NART is appropriate for use in a Parkinson's Disease population because it takes only a few moments to administer and it does not include any components that require motor skills based interaction from the participant. The crystallised intelligence domain that is measured is based on language skills which are not affected by the progression of Parkinson's Disease or other dementias (Christensen et al., 2007).

The NART has been validated against the WAIS and has been shown to be a valid and reliable measure. Outcomes of the NART have been compared with the WAIS in control samples and have shown to correlate highly (Nelson & Willison, 1991). This

indicates that the NART is measuring the same underlying construct as the WAIS while removing the effects of pathology or injury on the construct.

The NART has been used in several studies as a measure of pre-morbid IQ, both in general dementia populations and in PD populations. Previous studies investigating cognitive reserve in PD, Armstrong et al. (2010), Koerts, L. Tucha, Lange and O. Tucha (2013) and Pai and Chan (2001) have all used the NART as a measure of pre-morbid IQ in the PD population.

An Australian version of the NART, the AUSNART, has been developed (Hennessy & Mackenzie, 1995). While the population of this study consisted of Australians, the volume of research around the NART and its use in research in the PD population led to its selection ahead of the AUSNART in this study.

Brixton Spatial Anticipation Test

The Brixton Spatial Anticipation Test requires participants to predict a picture in a sequence based on previous values in a sequence of similar pictures. The test employs a constantly changing rule set to assess participant's executive function in terms of their planning and reactivity to changes in the sequence. The number of incorrect responses are tallied and compared to norms to provide a measure of the participant's executive function ability.

The Brixton Spatial Anticipation Test is relatively quick to administer and does not require any motor components, only requiring participants to view pictures and provide verbal responses to the assessor. This makes it a useful tool to use to obtain a measure of executive function ability in a Parkinson's Disease population.

BIRT Memory and Information Processing Battery

The BIRT Memory and Information Processing Battery (BMIPB) provides a quantitative measure of an individual's processing speed that allows for the effect of the person's motor speed. It does this by having the participant perform two tasks, one which asks them to cross out all the multiples of 11 in a row of 5 numbers within a time limit and then providing a similar task that requires them to cross out an 11 in a similar grid structure, but with only the number 11 shown in each row. The scores for each of these tasks are then combined to provide a measure of an individual's processing speed that is moderated based on their motor speed as measured by the second test.

The BMIPB only requires a short time to administer, and the allowance that it makes for motor speed in determining information processing speed makes it a useful measure for use in Parkinson's Disease populations. While information processing speed is not thought to be affected directly by disease progression it can have an effect on an individual's performance on tests of cognitive ability and hence it is a useful construct to measure in research involving cognition.

Measuring Cognitive Decline

In order to test the cognitive reserve theory a measure of change in cognition must be determined for comparison between participants. It is not enough to compare current level of functioning, as this would assume that all participants began at a similar level of functioning which is not the case in any real population based study. Ideally, change in cognition would be measured in a longitudinal fashion, with a baseline measurement taken before the onset of the disease and another taken at some point during the disease's progression. This is simply not a realistic approach however; it would require some knowledge of which individuals are likely to develop Parkinson's Disease before they are diagnosed with it and then waiting for a number of years to assess their functioning post

disease onset. Currently the best predictors of Parkinson's Disease are hereditary relationships and hence this type of research could require a generational type timeframe to identify and test participants.

Given, then, that a pre-morbid cognitive assessment is unlikely to be present for many, if any, individuals with Parkinson's Disease and the limitation of reasonable time periods on research, a baseline measure of cognitive functioning must be obtained in another manner. One way to achieve this is by using a measure of pre-morbid IQ that is not affected by the disease progression to provide a baseline assessment of cognitive ability. Therefore, when a prior measure of IQ is not available, cognitive decline can be measured by using a measure that gives an indication of pre-morbid IQ compared to a measure of current function (Paolo, Troster, Ryan & Koller, 1997). The NART provides just such a measure of pre-morbid IQ in the Parkinson's Disease population. The RBANS has been validated for use in sub cortical populations, including people with Parkinson's Disease, and therefore provides a useful measure of current functioning in the population (Randolph, 1998).

Both the NART and the RBANS provide a measure of IQ that is normalised around a mean of 100 and a standard deviation of 15 allowing direct comparison between the measures. While the measures have not been tested directly to assess that they are measuring the same construct, each has been validated against the WAIS and demonstrate that they are measuring the same IQ construct measured by that instrument. While this is imperfect it is reasonable to assume that the RBANS and the NART measures of IQ and pre-morbid IQ respectively can be compared to give a measure of change in cognitive function.

Factors Affecting Cognition

There are a number of demographic factors that have been demonstrated to affect cognition, or at least performance on cognitive assessments, in previous research. These include factors such as age and sex, and these should be recorded and examined in a research project involving cognition (de Lau & Breteler, 2006). Weintraub and Burn (2011) indicated that in the PD population males often experience greater cognitive decline, and females experience higher levels of depression. Additionally, given that decline in cognitive function is a known aspect of Parkinson's Disease it is worthwhile recording the amount of time that the individual has experienced disease pathology and hence the amount of time that the disease has been causing damage to their brain.

The effect of aging on cognition is well documented with a clear decline demonstrated in several cognitive functions as age progresses. These differences in cognition that are present due to normal aging are accounted for within at least some of the measures used in this study. The RBANS, for example, has normative data based on age groupings and scores that are determined for this study use these norms to reduce the effect of changes in cognition as a result of aging. Nevertheless, such normative data is not available for all of the measures used. Significantly, the normative data for the NART used in the study does not take age into account. In this case, the effects of aging on cognition could potentially skew the results of the research and hence age needs to be recorded and its effects examined and accounted for.

Similarly, cognitive abilities differ between the sexes. Specifically, males typically score higher than females in the visuospatial domain and females score higher than males in the language domain.

Parkinson's Disease is a degenerative condition and hence it would be anticipated that deficits in cognition would become worse over the course of the disease. However, much of the research into cognitive decline and Parkinson's Disease is contradictory in nature, with some studies suggesting that disease duration is unrelated to cognitive decline while others suggest that it correlates highly with length of disease duration (Tremblay, Achim, Macoir & Monetta, 2013).

6.2.3 *Materials*

The National Adult Reading Test (NART; Nelson & Willison, 1991)

The NART is a 50-item phonetically irregular word list presented in order of increasing difficulty (Appendix A1). Participants are asked to read the list of words aloud and the number of errors that they make is recorded. The words cannot be pronounced by common rules of pronunciation such as phonetic decoding. Total errors are then compared against norms to give an estimate of IQ.

Repeatable Battery for the Assessment of Neuropsychological Status (RBANS; Randolph, 1998)

The RBANS is a cognitive screening assessment which measures several cognitive domains (Immediate Memory, Visuospatial, Language, Attention, and Delayed Memory) across 12 subtests (list learning, story memory, figure copy, line orientation, naming, semantic fluency, digit span, coding, list recall, list recognition, story memory recall and figure recall). These items are scored individually to provide index scores across the five domains which are then used to provide an overall standard score. It has several parallel forms meaning that it can be given to the same participant repeatedly to assess change.

Australian normative data was used for data comparison, as developed by Green et al. (2008).

Wechsler Adult Intelligence Scale, 3rd ed, Digit Span Subtest. (WAIS-III Digit Span, Wechsler, 1997)

The Digit Span test from the WAIS (revision 3) was used in this study rather than the test from the RBANS. This task, which is more commonly used as one of the core subtests of the Wechsler Adult Intelligence Scale- III assesses immediate attention span and working memory by asking participants to immediately recall increasingly larger strings of numbers firstly in order, then backwards until the participant gets two strings of the same length incorrect.

The Brixton Spatial Anticipation Test (Brixton, Burgess & Shallice, 1996)

The Brixton examines visual concept formation and reasoning using 56 items to examine whether participants can recognise rules that account for pattern variations. This test has been found to have age effects with those in their 60's and 70's performing worse than those in their 20's (Lezak et al., 2004) This test assesses executive function.

Birt Motor and Information Processing Battery (BMIPB - Information Processing Task A; Coughlan, Oddy & Crawford, 2007)

The Birt Motor and Information Processing (BMIPB) examines participant's processing speed across two tasks, one which is designed to measure motor speed and one

which is designed to measure overall processing speed. The results on these two tasks are then matched together to give an adjusted processing speed score that compensates for difficulties in motor function.

FAS Verbal Fluency (Benton & Hamsher, 1989)

The FAS verbal fluency test measures an individual's ability to generate language. The test asks participants to list as many words as they can that begin with a particular letter (F, then A, then S) in a one minute period. The number of real and distinct words is then assessed and measured against normative data to give an indication of the functional level of the individual.

6.2.4 Procedure

Participants were administered a battery of assessments including the National Adult Reading Test, the Brixton Spatial Anticipation Test and the Repeatable Battery for the Assessment of Neuropsychological Status. The Digit Span test of the RBANS was replaced by the Wechsler Adult Intelligence Scale Digit Span Subtest (third edition). Most participants completed the entire interview in a single session, though in some cases it was necessary to split the interview across two sessions. Additional demographic variables, age, sex, disease duration and education level were also recorded as part of the interview.

Assessments were conducted by trained research assistants at the Royal Hobart Hospital. Training of the assessors was conducted by a trained Neuropsychologist in the administration of all assessment tools. Standardised administration and scoring, as outlined in respective manuals, was adhered to and age-based norms were used in scoring

where they could be sourced. All assessments were reviewed for accuracy by a trained clinical psychologist.

6.2.5 *Design and Analysis*

An additional variable, cognitive decline, was calculated from the instrument results collected in the study. This variable was used to indicate change in cognitive function from pre-morbid to current functioning. This variable was calculated by subtracting current IQ level (as measured by the RBANS) from estimated pre-morbid IQ level (NART IQ) and dividing the result by the pre-morbid IQ and multiplying by 100 to give decline as a percentage of original function. E.g. An individual with a NART score of 125 and a RBANS score of 100 would have a cognitive decline score of $(125 - 100) / 125 * 100$ or 20% decline. This decline measure was used to measure change of cognition in further analyses in this study.

NART groupings were created in two different ways to assess relationship with cognitive decline. The NART-TriSplit variable was created to split the sample as evenly as possible giving the maximum number of participants to each group. This resulted in three groupings of 29, 28 and 28 participants respectively. These groups represented NART scores of < 102, 102 – 112, and > 112. A univariate analysis was run with NART-TriSplit as the independent variable and cognitive decline as the dependent variable to analyse between groups effects.

The NART-SDGroup was created by placing participants in groups by standard deviation around the normal mean on the scale. That is, groups were created for individuals with NART scores 60 – 85, 85 – 100, 100 – 115 and 115 – 130. Note that for the purposes of avoiding duplication, individuals who landed on the borderline were put into the higher group, e.g. an IQ of 100 would place a participant in the 100-115 group. The

group sizes in this variable were 2, 20, 42, and 20 respectively. A univariate analysis was run with NART-SDGroup as the independent variable and cognitive decline as the dependent variable to analyse between groups effects. Estimated marginal means were calculated to demonstrate the direction of effects.

Education level was split into groups based on the level of schooling completed. Individuals were grouped based on primary to high school (education ≤ 10), college (education 11-12) or tertiary (education ≥ 13) giving group sizes of 43, 9 and 32 respectively. A univariate analysis was run with education group as the independent variable and cognitive decline as the dependent variable to determine between groups effects. Estimated marginal means were calculated to demonstrate the direction of effects.

Previous research has demonstrated that Education and NART scores are highly correlated. To confirm the relationship in the current research, a univariate analysis was run with Education group as the independent variable and NART score as the dependent variable.

Age groups were calculated for participants based on those participants who were under the age of 65 years and those who were 65 or over. This cut off was chosen to correspond with the life stages in the Lifetime of Experiences Questionnaire that will be discussed further in Study 2. This split gave groups of 24 and 60 participants respectively. Differences in decline between age groups were assessed using a t-test with age group as the independent variable and cognitive decline as the dependent variable.

Decline scores were calculated for a number of the individual measures in a similar fashion to overall cognitive decline. Where the score was not standardised around a mean of 100 and a standard deviation of 15, conversions were calculated to produce scores of this type to allow comparison with NART scores. These comparisons were made for the

RBANS Immediate and delayed memory composite indexes, the Brixton spatial anticipation test, the BIRT memory and information processing battery standard, motor and adjusted scores, WAIS digit span, FAS test of semantic fluency, Trail making test parts A and B, and the line orientation and list recognition sub tests of the RBANS. In each case the decline score was calculated as (NART score – standardised test score) divided by NART score. These decline scores were then analysed against NART-TriSplit groups using an analysis of variance to determine whether or not pre-morbid IQ predicted reduction in decline.

Standardised scores were also compared to NART TriSplit groups to determine whether initial cognitive level / score had an effect on the individual's measured cognition with the disease. Standard scores were examined against NART TriSplit groups using analyses of variance for the Brixton Spatial Anticipation Test and the BMIPB Adjusted measures.

An age-of-diagnosis score was calculated for each participant by taking their current age and subtracting their disease duration. This was then analysed against NART-TriSplit groups using an analysis of variance to determine whether estimated pre-morbid IQ has an effect on the age of diagnosis.

6.3 Results

Univariate analysis of NART-TriSplit with cognitive decline did not result in a significant relationship ($F(2,81) = 2.643, p = 0.077$). The means plot (Figure 2) demonstrated that the direction of the relationship was positive, opposite to that which had been hypothesised.

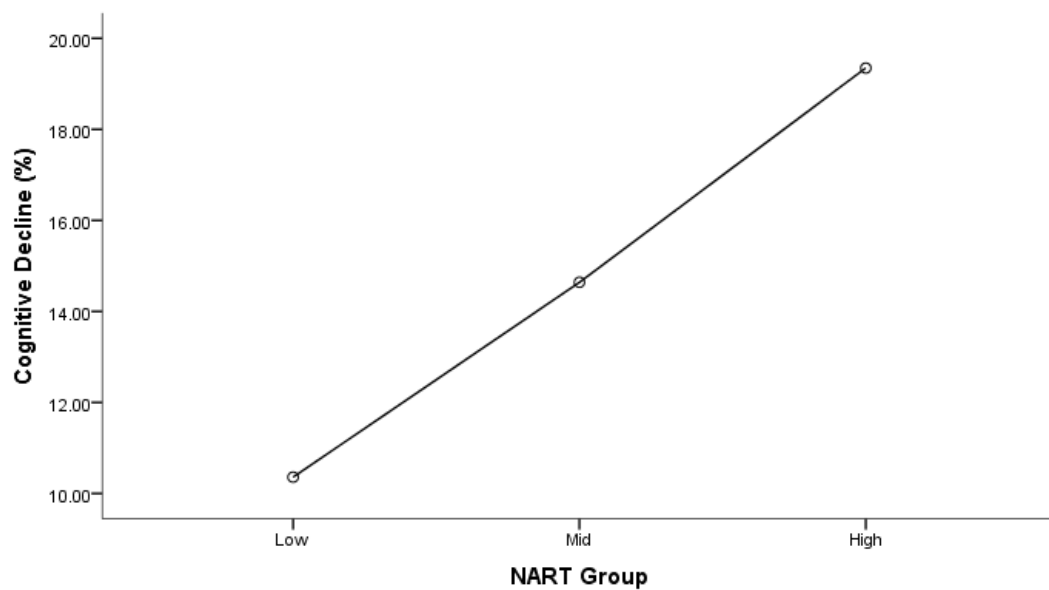


Figure 2. NART 3-way split group means for Cognitive Decline

Analysis of the same effect with the NART split into four groups (<85, 85-100, 100-115, 115+) rather than three similarly did not demonstrate a significant relationship with cognitive decline ($F(3,80) = 0.888, p = 0.451$) and nor did education group ($F(3,80) = 1.295, p = 0.282$).

Univariate analysis to check whether the NART and Education measures were measuring the same construct as anticipated revealed a significant positive relationship between NART and Education group ($F(2,82) = 16.645, p = 0.000, \eta^2 = 0.289$) with the three education groups (high school, college, tertiary) as the independent variable. This indicated

that the measures were related as anticipated with an increase in education level associated with an increase in NART score. Mean NART scores for each of the education groups are shown in Figure 3.

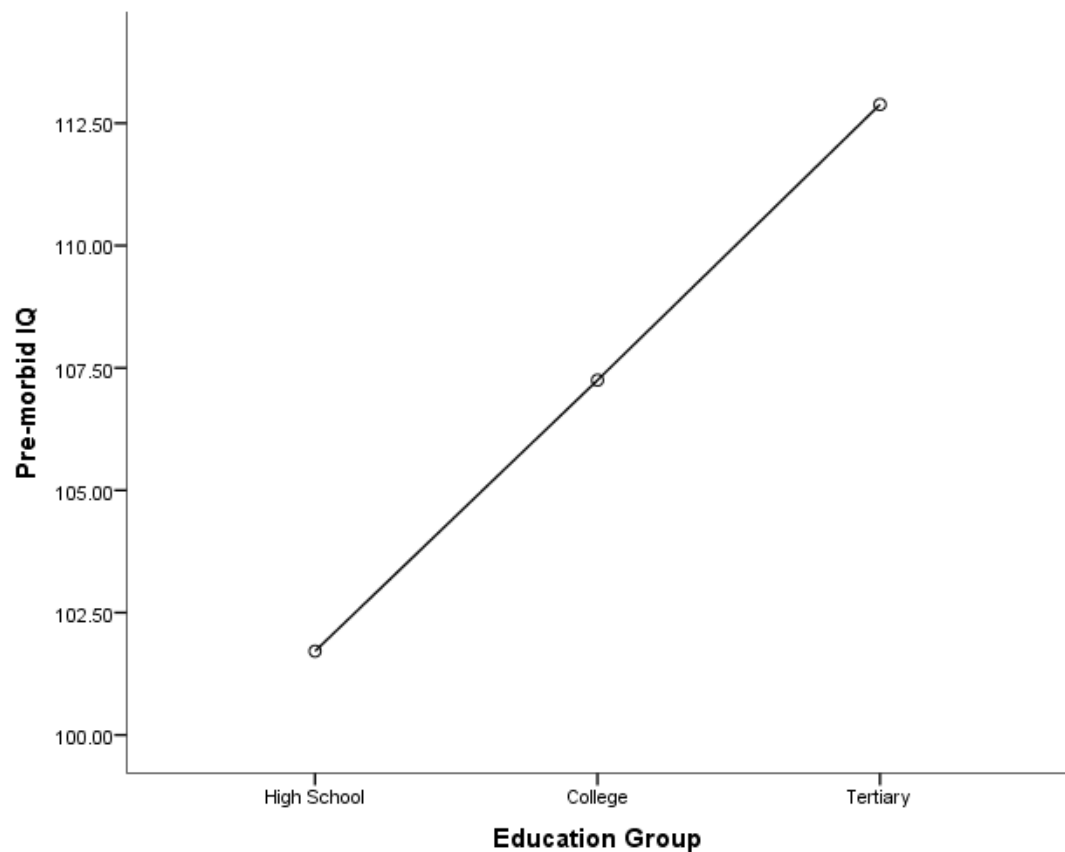


Figure 3. Mean NART scores by Education Group

Analysis of age effects revealed a significant relationship between age group and cognitive decline ($F(1,82) = 7.889, p = 0.006, \eta^2 = 0.088$). Univariate analyses to check age group relationships with RBANS total score ($F(1,84) = 7.441, p = 0.008, \eta^2 = 0.081$) and NART IQ score ($F(1,83) = 1.390, p = 0.242$) were performed to check the reliability of this result. Estimated marginal means for each age group for each of these analyses is given in Table 1.

Table 1
Mean Cognitive Scores for Age Groupings

Age Group	Mean Decline (%)	Mean RBANS Total	Mean NART FSIQ
Under 65	8.1	95.0	104.6
65 and Over	17.6	85.0	107.3

Based on these results, analyses of relationships for NART-TriSplit and Education group against cognitive decline were performed again using age group as a covariate. Both the NART-TriSplit ($F(3,80) = 4.261, p = 0.008, \eta^2 = 0.138$) and the Education group ($F(4,79) = 3.089, p = 0.020, \eta^2 = 0.135$) demonstrated significant relationships with cognitive decline when age group was included as a covariate.

Table 2
Means for NART Tri-Split Groups with Age Group as a covariate

NART Tri-Split Group	Mean Cognitive Decline (%)	Std Error
1 (< 102)	10.557	2.719
2 (102 – 112)	15.067	2.535
3 (> 112)	18.706	2.630

Table 3
Cognitive Decline by Education Group with Age Group as a covariate

Education Group	Mean Cognitive Decline (%)	Std Dev
Primary to High School	13.35	14.93
College	20.21	15.80
Tertiary	15.44	14.01

Significant relationships were demonstrated between NART-TriSplit groups and several of the tests measured. The results of the analyses are summarised in Table 4. Consistent with the overall analysis, these significant relationships, with line orientation and delayed memory, demonstrated that greater decline was associated with higher levels of pre-morbid functioning.

Table 4
Test score relationships with NART TriSplit groups

Measure	df	F value	η^2	Significance (<i>p</i>)
RBANS Immediate Memory	2,82	0.234	0.006	0.792
RBANS Line Orientation	2,81	8.025	0.185	0.001
RBANS Delayed Memory	2,82	3.975	0.088	0.023
RBANS List Recognition	2,80	4.214	0.095	0.018
WAIS Digit Span	2,82	0.900	0.021	0.411
FAS Semantic Fluency	2,82	4.172	0.092	0.019
Brixton Spatial Anticipation Test	2,76	9.155	0.194	0.000
BIRT Information Processing	2,71	19.430	0.354	0.000
BIRT Motor Speed	2,75	8.991	0.193	0.000
BIRT Adjusted	2,71	18.000	0.336	0.000

Follow up analysis of BMIPB adjusted scores (rather than change in scores) for each of the NART TriSplit groups was run to determine the underlying cause of the significance of the relationship. The analysis did not demonstrate a significant relationship. Means, maxima and minima for each of the groups are shown in Table 5. Note that values have been adjusted to the standard scale (mean 100, std dev 15) for ease of comparison.

Table 5
BMIPB Adjusted x NART TriSplit group descriptive data

Pre-Morbid IQ Group	N	Mean	Std Dev	Minimum	Maximum
1 (< 102)	23	85.0	13.73	60	110
2 (102 – 112)	26	86.9	9.28	70	115
3 (> 112)	25	83.2	12.82	60	110

Similar analysis for the Brixton Spatial Anticipation Test with NART TriSplit groups gave a very similar non-significant result. Descriptive data is shown in Table 6.

Table 6
Brixton Spatial Anticipation Test x NART TriSplit group descriptive data

Pre-Morbid IQ Group	N	Mean	Std Dev	Minimum	Maximum
1 (< 102)	25	64.6	9.78	55	85
2 (102 – 112)	29	70.7	10.75	55	90
3 (> 112)	25	67.0	11.55	55	85

The relationship between NART Group and age of diagnosis was insignificant ($F(2,82) = 0.618, p = 0.541$). Nevertheless, the means of the groups, shown in Table 7, indicate that mean age of diagnosis increases with pre-morbid IQ. This information may be misleading, however, as the relationship is statistically insignificant.

Table 7
Age of Onset Means for NART TriSplit Groups

NART TriSplit Group	Mean Age of Onset	Std Dev
1 (<102)	60.3	11.44
2 (102-112)	62.1	8.65
3 (112+)	63.3	9.70

6.4 Discussion

Contrary to hypothesis one, higher pre-morbid IQ was not associated with reduced decline in cognition. In fact, while initial analyses did not produce a significant relationship, examination of means indicated an inverse relationship where those individuals with higher pre morbid IQ experienced the largest loss in cognitive functioning across all cognitive domains. This relationship was later confirmed using age group as a covariate. Previous research into cortical dementias (AD) found that those with higher pre-morbid IQ experienced less cognitive deterioration and slower developing disease progression than their counterparts with lower pre morbid IQ; the opposite result to the findings of this study. However, cognitive reserve has seldom been studied in sub-cortical populations so it may be that the relationships identified in said research simply do not hold in sub-cortical dementia populations. Interestingly this finding is in broad agreement with Pai and Chan (2001) who found a similar inverse relationship between cognitive decline and education in PD.

One possible explanation for this inverse relationship may be that those with a higher pre-morbid IQ have more cognitive ability to lose and that any cognitive deterioration that does occur may be more pronounced than the deterioration that occurs at a lower level. This phenomenon may be explained by Wilder's law of initial values which postulates that those with more of 'something' have more to lose hence demonstrate greater loss than those with little to lose (Wilder, 1967). This explanation is reinforced by the fact that measures such as the BMIPB and Brixton demonstrate relationships between decline and pre-morbid IQ but not between test scores and pre-morbid IQ. That is, lower pre-morbid IQ does not relate to lower performance on the Brixton, but higher change in cognitive functioning is related to lower performance. Another possible explanation for

this relationship is that it is a type I error, though the effect size demonstrated falls into the large category and hence this seems unlikely. The current findings suggest that regardless of initial IQ, individuals who experience Parkinson's Disease end up with a similar, reduced, level of functioning. Accordingly it appears on present results that those who have a higher pre-morbid IQ experience a larger decline to the same level as those with a lower pre-morbid IQ. This is a strong indication of a lack of cognitive reserve, at least measured by pre-morbid IQ, on these indexes in this population.

Consistent with these findings for pre-morbid IQ, analyses demonstrated that individuals with higher levels of education experienced more decline than those with lower levels of education, contrary to hypothesis 2. Education is an established measure of cognitive reserve in cortical dementias and correlates highly with another established measure in pre-morbid IQ, hence this result is also unexpected. Like the pre-morbid IQ relationship, initial analysis did not demonstrate a significant relationship, rather a weak trend in increasing means. Adding age group as a covariate, however, confirmed the significance of the relationship. It should be noted that the effect size for this relationship was slightly lower than that with pre-morbid IQ, with the education relationship falling into the medium category. However, given the result with pre-morbid IQ and the high correlation between pre-morbid IQ and education the presence of this relationship is not surprising. Nevertheless, it does lend weight to the existence of the relationship due to the fact that the level of education completed is a straight forward demographic measure and not an abstractly measured concept like pre-morbid IQ. There is also existing research to support this relationship with Pai and Chan (2001) demonstrating the same education effect among their PD sample. However, the implication that obtaining higher levels of education is detrimental to an individual who contracts Parkinson's Disease is implausible, hence this is likely also attributed to the law of initial values argument that an individual with more to lose will lose more.

One aspect of the education group analysis that should be noted is that the relationship between education and cognitive decline is not as clearly demonstrated in the group means as it is for pre-morbid IQ. In fact, the college group has the highest mean decline, higher than the tertiary group, as can be seen in Table 3. This could be explained by the comparatively low numbers of participants that fell into the college group, with the majority either leaving after high school or going on to tertiary education; a representation of educational opportunities available to the sample population for the relevant age group. The error terms in the smaller group is far higher, and hence the relationship is based on the relationship of the means of the high school and tertiary groups which demonstrate a large mean difference with those receiving tertiary education experiencing more decline.

Another consideration is that education may be flawed as a proxy for IQ due to inconsistent access to it based on gender and socio-economic status. These factors can create artificial discrepancies between otherwise similar individuals depending on their varying access to educational opportunities. Education correlated highly with pre-morbid IQ in this study and hence it is likely that individuals have had similar educational opportunities. This suggests that in this study at least this issue may have been avoided. Nevertheless it is important to consider this possibility when using education as a predictive measure of decline rather than as a retrospective comparison measure.

A systematic review by Hindle, Matyr and Clare (2013) that examined cognitive reserve in PD stipulated that a good measure of cognitive reserve should have a beneficial effect when examined cross sectionally, produce a slower rate of decline and not prevent, but rather slow the onset of dementia in PD. Despite the evidence for an inverse effect with those with lower IQ experiencing less severe cognitive deterioration there was evidence in the current study to suggest that those with a higher pre-morbid IQ experienced a later disease diagnosis. This supports the notion that while IQ does not act

as a means of protection once disease onset has occurred, it may ward off or slow the development of the disease in its initial stages.

Beyond the above, the findings of this study of cognitive reserve contradict the findings in much AD literature that premorbid IQ and education are associated with reduced cognitive decline. There are, however, some previous studies that have indicated cognitive reserve in the Parkinson's Disease population. Koerts et al. (2012) for example demonstrated that cognitive reserve existed in a sample of 48 people with Parkinson's Disease. However, these studies determined "reserve" differently to the current study. Koerts et al. delineated their sample into pre-morbid IQ groups and then looked at the percentage of each group that experienced impairment, where impairment was defined as a score on a measure that was 1.5 standard deviations below the mean. For example, if considering the RBANS FSIQ, this would mean that anyone who scored below 77.5 was defined as impaired. They demonstrated that individuals with higher pre-morbid IQ reached these impairment thresholds later than those with lower pre-morbid IQ and indicated that this was proof of cognitive reserve. An aspect of this that needs to be considered is that a person with a pre-morbid IQ of 77 who remained at 77 in current testing would indicate an impairment in the low IQ group and hence would be interpreted as showing decline without having actually lost any function. At the same time, and individual who had a pre-morbid IQ of 125 and a current IQ of 78 would be deemed not to have experienced a reduction in function. This does not demonstrate protection against decline per se, but rather protection against reaching a measured threshold to define an individual as impaired; i.e. if an individual is higher functioning to begin with they are less likely to reach a level of incapacity than someone who begins at a lower level of functioning.

Similarly, Armstrong et al. (2012) demonstrated reserve by measuring the percentage of pre-morbid IQ groups who were diagnosed with Mild Cognitive Impairment (MCI). As with Koerts et al. (2012) however, the diagnosis of MCI required a score at or below 1.5 standard deviations below the mean on one of the administered cognitive measure, biasing the diagnosis toward those with lower pre-morbid function.

It is suggested that the threshold based approach to index “cognitive reserve” used by Koerts et al. (2012) and Armstrong et al. (2012) results in a group effect whereby all individuals are treated equally at end point regardless of their pre-morbid function. A strength of the current study is that it utilises an ipsative approach. That is, it looks at individual discrepancies between premorbid functioning and ‘current’ functioning on measures across several cognitive domains. Individual differences are tremendously important to examine in PD as individuals differ substantially in the clusters of symptoms they experience, hence the type and degree of cognitive impairment they encounter. One other study of cognitive reserve in PD that has taken an individual differences approach, Pai and Chan (2001), demonstrated a similar result for education to that seen in the current study. The study compared current cognitive performance, measured by the CASI, with formal education level and found that individuals demonstrated similar levels of functioning regardless of their education level. While this is not a direct pre and post comparison, education is often considered to be a proxy measure of pre-morbid IQ, and hence it would be anticipated that participants with higher education levels would have had higher levels of cognitive functioning prior to the progression of the disease. This lack of a protective relationship is supported by the findings of the current study.

6.5 Limitations

The method of calculating decline as a difference in NART and RBANS scores introduces a potential error; while both the NART and the RBANS have been shown to correlate highly with the results of the WAIS and both measure IQ on the same scale there remains the possibility that the outcomes of the scales are not tightly related enough to accurately measure change in cognitive function in this manner. Investigation into the relationship between NART scores and RBANS scores in a control population would be beneficial to further justify the use of these measures as effective pre and post comparison tools. Further, this ideally needs to be extended into a Parkinson's Disease population, before disease can affect cognition, to confirm the comparison in this population. This, however, is impractical if not impossible.

The most robust method of testing cognitive reserve is to have both pre and post measures – e.g. before an individual has surgery or experiences a TBI. However, unless an individual has participated in a study prior to the onset of their dementia it is near impossible to conduct pre and post dementia research meaning that the majority of research examining cognitive changes in dementias has to employ a cross sectional or longitudinal study design. Most studies examining cognitive reserve tend to employ a cross sectional research design as longitudinal designs become difficult. Due to the advanced age of many participants attrition is an issue with many participants becoming too disabled by their disease process to participate in further research or passing away before follow up occurs. Cross sectional research allows researchers to get higher study numbers. However, the issue in employing this design is the difficulty in finding measures that are robust.

To investigate the demonstrated relationships further it would be useful to conduct a longitudinal study allowing the same measure to be administered as a starting point and

a change in function, and, given the repeatable nature of the RBANS, the data in this study could potentially be used as the baseline data for such a comparison.

Chapter 7: Study Two – Demographics, Life Experience and Parkinson's Disease

7.1 Aim and Hypotheses

This study investigated the possibility that pre-morbid demographic factors and life experiences might affect cognitive decline in people with Parkinson's Disease. The fundamental reasons for the research were both to identify factors in the participant's history that may contribute to protection against decline, and to identify any activities associated with a slowing of cognitive decline once PD has been diagnosed. Factors such as exercise, for example, have been identified as moderating variables in Alzheimer's Disease populations and hence should be investigated with Parkinson's Disease populations.

Based on the previous reviewed research, it was hypothesised that:

1. Age will have a positive relationship with decline such that cognitive decline increases as the disease progresses.
2. Disease duration will have a positive relationship with decline such that decline increases over time as the disease progresses.
3. There will be no difference in the decline process between males and females.
4. Individuals with higher levels of life experience will demonstrate less severe cognitive decline.
5. Participation in physical activity, particularly post diagnosis, will have a positive effect on cognition.

7.2 Methodology

7.2.1 Participants

This study was investigated using data collected from the same research group as in studies one. For information on participants in the study please see study one (section 6.2.1).

7.2.2 Selection of Measures

The rationale for the selection of the cognitive measures chosen for this study is the same as has been stated in section 6.2.2.

7.2.3 Materials

The following materials were used that were also used in the first study. Please refer to the materials section of study one for full details.

- *The National Adult Reading Test (NART; Nelson & Willison, 1991)*
- *Repeatable Battery for the Assessment of Neuropsychological Status (RBANS; Randolph, 1998)*
- *Wechsler Adult Intelligence Scale, 3rd ed, Digit Span Subtest. (WAIS-III Digit Span, Wechsler, 1997)*
- *The Brixton Spatial Anticipation Test (Brixton, Burgess & Shallice, 1996)*
- *Birt Adult Memory and Information Processing Battery (BMIPB - Information Processing Task A; Coughlan, Oddy & Crawford, 2007)*
- *FAS Test of Verbal Fluency (Benton & Hamsher, 1989)*

Life Experiences Questionnaire (LEQ; Valenzuela & Sachdev, 2007)

The LEQ (Appendix A) is a questionnaire that measures an individual's level of participation in activities during their lifetime, with a focus on cognitively stimulating activities. Participants are asked to fill out the questionnaire which examines individual's lifetime participation across three time periods, young adulthood (<30 years old), middle age (30-65 years old) and later life (65+ years old). The LEQ is then scored to provide a quantitative rating across the three time points.

7.2.4 Procedure

The battery of neuropsychological assessments was administered as per study one (section 6.2.4).

7.2.5 Design and Analysis

As in study one, an additional variable, cognitive decline, was calculated from the instrument results collected in the study. This variable was used to indicate change in cognitive function from pre-morbid to current functioning. This variable was calculated by subtracting current IQ level (as measured by the RBANS) from pre-morbid IQ level (NART IQ) and dividing the result by the pre-morbid IQ and multiplying by 100 to give decline as a percentage of original function. For example, an individual with a NART score of 125 and a RBANS score of 100 would have a cognitive decline score of $(125 - 100) / 125 * 100$ or 20% decline. This decline measure was used as to measure change of cognition in further analyses in this study.

Additional variables were calculated to facilitate analysis of Lifetime of Experiences Questionnaire (LEQ) results and demographic variables.

- **LEQ Young Adult Overall** was calculated by summing the values of the general section questions of the young adult section of the LEQ. The general section questions refer to the questions that are rated on regularity, between never and daily, and are repeated at each life stage in the questionnaire.
- **LEQ Mid Life Overall** was calculated by summing the values of the general section questions of the mid-life section of the LEQ.
- **LEQ Late Life Overall** was calculated by summing the values of the general section questions of the late life section of the LEQ.
- **LEQ instrument played** was calculated at each life stage by determining whether or not the frequency of instrument playing was more frequently than monthly at that life stage. This was used to split the sample into those who regularly played an instrument and those who did not.
- **LEQ age group** was used to split participants into groups at each of the LEQ life stages (≤ 30 , 31-64, 65+). There were no participants below the age of 44, hence the first of these groups was empty.
- **Education group** was used to classify participants into those who finished school at primary, secondary, college or tertiary levels.

Pearson's correlations were used to determine the direction of relationships between LEQ overall scores at each life stage and cognitive decline. Correlations were examined for negative values of a size that was deemed worthy of further investigation (initially, ≤ -0.2). The negative correlation indicates that as the index score increases cognitive decline decreases and hence there is potential for that factor to be protective against cognitive decline.

Analyses of variance were used to analyse the effects of the general questions repeated at each of the life stages with RBANS total decline. In each case the LEQ scores were grouped in to three levels; Rarely (1-2), Sometimes (3-4) and Often (5-6). The questions that were analysed are:

- How regularly did you see your family (never [1] – daily [6])
- How regularly did you play an instrument (never[1] – daily [6])
- How regularly did you practice art (never [1] – daily [6])
- How regularly did you engage in sport at a mild level (never [1] – daily [6])
- How regularly did you engage in sport at a moderate level (never [1] – daily [6])
- How regularly did you engage in sport at a vigorous level (never [1] – daily [6])
- How regularly did you read (never [1] – daily [6])
- How regularly did you practice speaking a second language (never [1] – daily [6])
- Did you travel (Yes [1] or No [2])
- Did you have other hobbies (Yes [1] or No [2])
- For Mid and Late life stages, did you engage in further study (Yes [1] or No [2])

Further analyses were performed for individual test performance and decline with LEQ factors at all life stages. These analyses were performed for each of the RBANS composite indexes, FAS Semantic Fluency, WAIS digit span, Brixton Spatial Anticipation test and BIRT Memory and Information Processing Battery adjusted scores. As in the overall decline analysis, LEQ scores were split into three levels. In each case the LEQ scores were

analysed with test performance and with decline on that test, calculated as (NART - test score) / NART.

Age groups were calculated based on those participants who were under the age of 65 and those who were 65 or over. This cut off was chosen to line up with the life stages in the Lifetime of Experiences Questionnaire. This split gave groups of 24 and 60 participants respectively. Differences in decline between age groups were assessed using a t-test with age group as the independent variable and cognitive decline as the dependent variable.

The effect of disease duration, measured in years since diagnosis, was determined through a univariate analysis with disease duration as the independent variable and cognitive decline as the dependent variable. Estimated marginal means were calculated to determine the direction of the effect. Disease duration was further examined against decline scores on individual measures; FAS, Brixton Spatial Anticipation Test, WAIS Digit Span and BMIPB adjusted scores. These were examined as univariate analyses of variance with duration and then duration group as the independent variable. Duration group was defined by grouping participants with duration less than 2 years, 2-5 years, 5-10 years and 10+ years. These duration group boundaries were selected to give the most even spread of participants across the groups.

RBANS total and NART FSIQ scores were also compared to disease duration using analyses of variance to determine whether outcomes on either of these measures changed over time; specifically time since diagnosis.

Sex differences were examined with a t-test examining between groups effects for males and females. Cognitive decline was used as the dependent variable. This analysis was repeated using an analysis of variance with age group as a covariate to account for the age differences between male and females. Estimated marginal means were calculated to

determine the direction of the effect. Tests of between group effects for sex were also calculated for RBANS total scores and NART scores, in each case using age group as a covariate.

7.3 Results

Correlations were examined between the calculated cognitive decline measure and each of the LEQ life stage overall scores.

Table 8
LEQ Overall Scores Correlated with Cognitive Decline

	LEQ Young Adult Overall	LEQ Mid Life Overall	LEQ Late Life Overall
Cognitive Decline	0.002	0.023	-0.143

Of the three overall scores, none demonstrated a significant correlation with the cognitive decline measure. Only the Late life overall score indicated a relationship in the protective direction; i.e. increase in late life activity being associated with lower levels of decline.

Analyses of variance were examined between each of the LEQ questions that applies at each life stage and cognitive decline to identify factors that have an effect on the decline process. Note that this result was also demonstrated using a multiple regression analysis, the output of which is included in Table C.6 in Appendix C. The factors that indicated a relationship in the protective direction are listed in Table 9.

Table 9
LEQ Items with significant relationships with Cognitive Decline

Factor and Life Stage	df	<i>F</i>	η^2	Significance (<i>p</i>)
Young Adult				
Playing an Instrument	2,76	3.189	0.077	0.047

Playing an instrument was the only index that indicated a significant relationship with overall decline at any life stage. To investigate the effect of playing an instrument

further, an additional variable was created that split the LEQ Instrument categories into two levels rather than three for each of the life stages. T-tests were then run to compare the means of the instrument playing and non-instrument playing group at each life stage.

Table 10
Mean Decline between Instrument Groups at each Life Stage

Life Stage	Mean (N)	Mean (N)	t-value	η^2	Significance (<i>p</i>)
	instrument ≤ 3	instrument > 3			
Young Adult	16.83 (62)	8.20 (17)	2.153	0.238	0.034*
Mid Life	16.63 (65)	7.60 (14)	2.086	0.231	0.040*

Table 10 shows significant relationships between regularly playing an instrument and a reduction in decline at both the young adult and mid phases of life. There was a small decline observed in the late life group, though this relationship was not significant. This is likely due to the fact that there was only one participant who regularly played a musical instrument later in life. A further analysis was conducted for groups who played an instrument at all in later life to those who didn't (instrument score > 1), but even this loosening of the group rules only brought the number in the instrument group up to 5 and did not demonstrate a significant relationship.

Time with family was inspected in a similar fashion to playing of a musical. Inspection of scores revealed that almost all participants had indicated that they had seen their family daily, the highest score possible, at all stages of life. The Late Life Family scores were split into two groups, one where participants had given the response of daily and one where they had given anything less and a t-test conducted on these two groups.

Table 11
Late Life Family Groups and Cognitive Decline

	Mean (N)	Mean (N)	t-value	Significance(p)
	Family = 6	Family < 6		
Late Life	12.2 (49)	20.94 (5)	1.173	0.246

Table 11 indicates that there is not a significant relationship between cognitive decline and time spent with family, though there is some indication that this may be limited by the number of participants in the study with less than daily contact with their families. It is possible, however, that this relationship is due to individuals with more decline being less able to contact or visit their families rather than their increased decline being a result of their lack of contact with their families.

Other items that showed correlations in Table 9 were also further analysed with t-tests but did not demonstrate significant relationships; Travel at Young Adult ($t = 1.611$, $p = 0.111$), further study at mid-life ($t = 0.916$, $p = 0.363$).

One other item that correlated with cognitive decline was moderate physical exercise in the mid-life stage (0.251 , $p = 0.026$), though this was a positive correlation and hence would indicate that individuals with higher exercise levels experience higher amounts of decline. This is a relatively small correlation and conflicts with previous research. The result was followed up with an analysis of variance for mid-life moderate exercise level which demonstrated no significant relationship ($p = 0.341$).

Correlations between individual test scores and LEQ scores demonstrated significant correlations between FAS and WAIS Digit span scores for playing an instrument at various life stages. These correlations are given in Table 12. As with RBANS total scores,

the effects are not seen in the late life group and this may be due to the small number of instrument players in that sample group.

Table 12
LEQ Instrument correlations at various life stages

	Young Adult	Mid Life	Late Life
FAS	0.262 ($p = 0.018$)	0.263 ($p = 0.018$)	-0.130 ($p = 0.350$)
FAS Decline	-0.239 ($p = 0.033$)	-0.294 ($p = 0.008$)	0.002 ($p = 0.991$)
WAIS Digit Span	0.171 ($p = 0.125$)	0.305 ($p = 0.005$)	0.069 ($p = 0.619$)
WAIS Digit Span Decline	-0.088 ($p = 0.436$)	-0.318 ($p = 0.004$)	-0.088 ($p = 0.529$)

WAIS digit span score was also significantly positively correlated with travel at the young adult life stage (0.311, $p = 0.004$).

The Brixton Spatial Anticipation Test decline only demonstrated one significant negative correlation with time spent with family in the late life stage (-0.446, $p = 0.001$). This result is most likely similarly due to group size limitations with almost all participants choosing the highest possible score on this index.

BIRT Memory and Information Processing Speed Battery adjusted speed decline had very few significant correlations with LEQ measures. The only significant negative correlation with decline was in the ambiguous “other hobbies” measure at a young adult age (-0.277, $p = 0.018$). This may be representative of other factors, not measured explicitly on the LEQ, that have an effect on Information Processing Speed in Parkinson’s Dementia.

An odd result was the significant negative correlation of late life participation in art with performance on the BIRT Motor and Information Processing Battery Adjusted score (-0.310, $p = 0.036$). This was investigated further with an analysis of variance that did not

demonstrate a significant relationship ($F(5,40) = 1.249, p = 0.305$), however the means plot (Figure 4) demonstrated a trend for the mean to be lower above the response score of 1; never undertake artistic pastimes. Participants were then split into two groups of those who had responded that they did not undertake any artistic activities in late life ($N = 28$) and those who participated in art at any regularity ($N = 18$). A t-test of the between groups effects demonstrated a significant relationship ($t = 2.572, p = 0.014, \eta^2 = 0.131$) with the group who participated in art activities having a mean BMIPB Adjusted Standard score an average of 9.29 points lower than participants who were not involved in artistic activities.

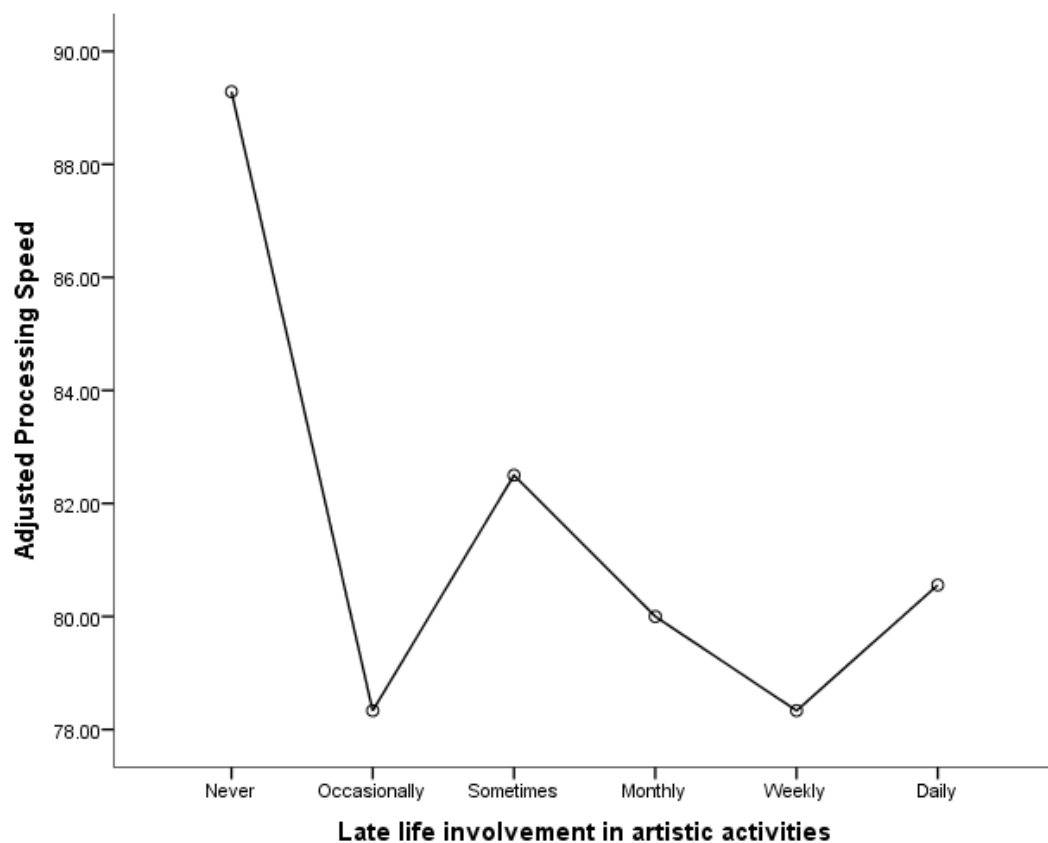


Figure 4. BMIPB Adjusted Mean Score by LEQ Late participation in art activities

7.3.1 Age

Age differences were examined using a one-way analysis of variance which did not demonstrate a relationship between age and cognitive decline. Note that this relationship was also demonstrated by a regression analysis, the result of which can be seen in Table C.1 in Appendix C. An additional variable was created to split participants into two age based groups (<65, 65+) based on which section of the LEQ life stages they were in (all participants were over the age of 30). The results of a t-test conducted on the groups are show in Table 13.

Table 13
Age Groups and Cognitive Decline

	Mean (N) Age < 65	Mean (N) Age 65+	t-value	Significance (<i>p</i>)
Cognitive Decline	8.06 (24)	17.61 (60)	-2.809	0.006*

7.3.2 Sex

Differences in cognitive decline were examined for males and females using a one way analysis of variance ($F(1,82) = 0.941, p = 0.335$). The result did not demonstrate a significant difference with female participants showing a slightly lower mean decline (13.09) than males (16.22). Note that this relationship was also analysed using a regression analysis with similar results that can be seen in Table C.1 in Appendix C.

A further analysis was run using the age group split as a covariate. This model demonstrated a significant difference between the sexes ($F(2,81) = 4.343, p = 0.016, \eta^2 = 0.097$). This indicates a significant difference in decline between males and females that may be obscured by differences in age in the group, with increased age also significantly linked with increased decline.

RBANS total score and NART FSIQ score were also analysed against sex groups with the former demonstrating a significant relationship ($F(2,83) = 7.863, p = 0.001, \eta^2 = 0.159$) and the latter a trend ($F(2,82) = 2.522, p = 0.087, \eta^2 = 0.058$). Means and standard deviations for these analyses are shown in Table 14, favouring females.

Table 14
Sex Difference in NART and RBANS Total Scores

Sex	NART		RBANS	
	Mean	Std Dev	Mean	Std Dev
Male	104.9	10.6	83.9	16.1
Female	108.8	8.0	93.1	13.6

7.3.3 Disease Duration

Disease duration did not demonstrate a relationship with cognitive decline ($F(30,53) = 0.992, p = 0.498$). This indicates a lack of change in function being related to pre-morbid position post diagnosis of the disease. Note that this relationship was demonstrate using a regression analysis, the result of which can be seen in Table C.1 in Appendix C.

Analyses of specific measures identified significant relationships between duration and RBANS total ($F(30,55) = 1.918, p = 0.018, \eta^2 = 0.511$), FAS Decline ($F(30,54) = 2.664, p = 0.001, \eta^2 = 0.595$) and WAIS Digit Span Decline ($F(30,54) = 1.921, p = 0.018, \eta^2 = 0.516$). However, the direction of these relationships is difficult to determine, as demonstrated in the means plots for RBANS Total (Figure 5) and FAS Decline (Figure 6).

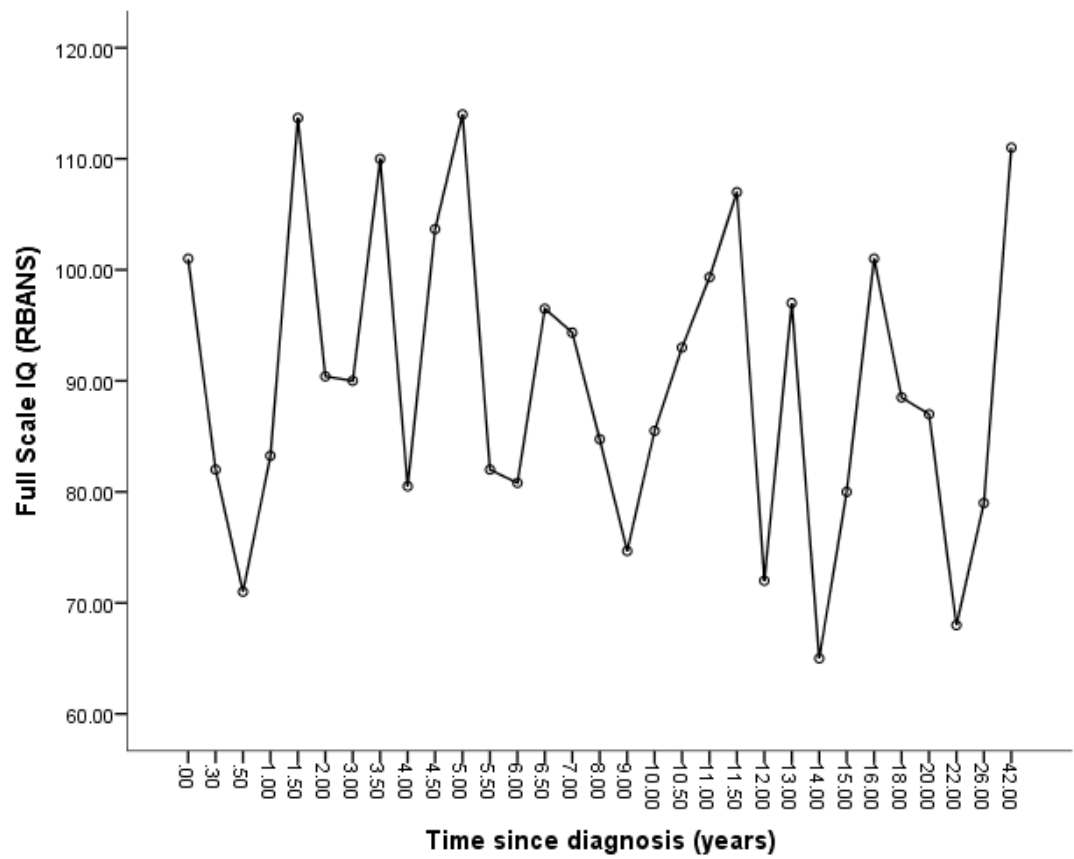


Figure 5. Means Plot for RBANS total compared to disease duration

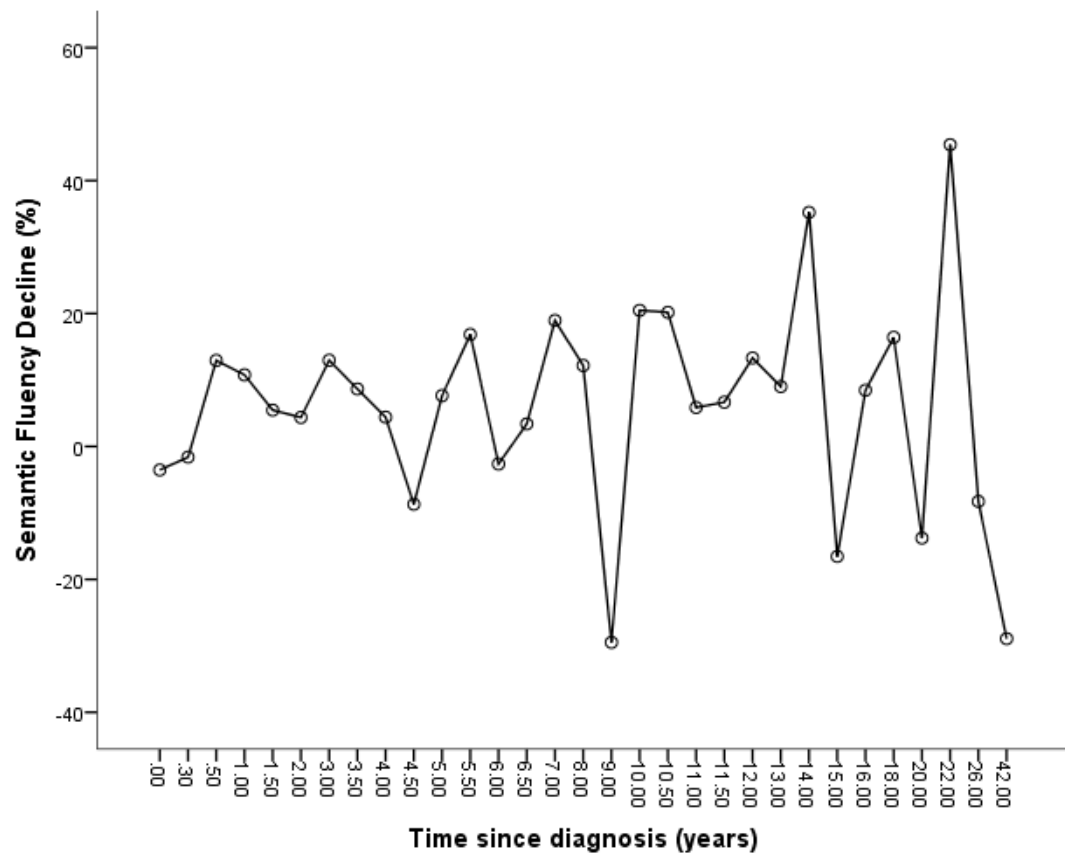


Figure 6. Means plot for change in FAS scores by disease duration

Duration was split into groups and these analyses re-run to determine whether the direction of the effect was any clearer. While the plots produced appear to clarify the direction for RBANS Total (Figure 7) at least, the relationship in this analysis was not significant ($F(3,82) = 0.701, p = 0.554$).

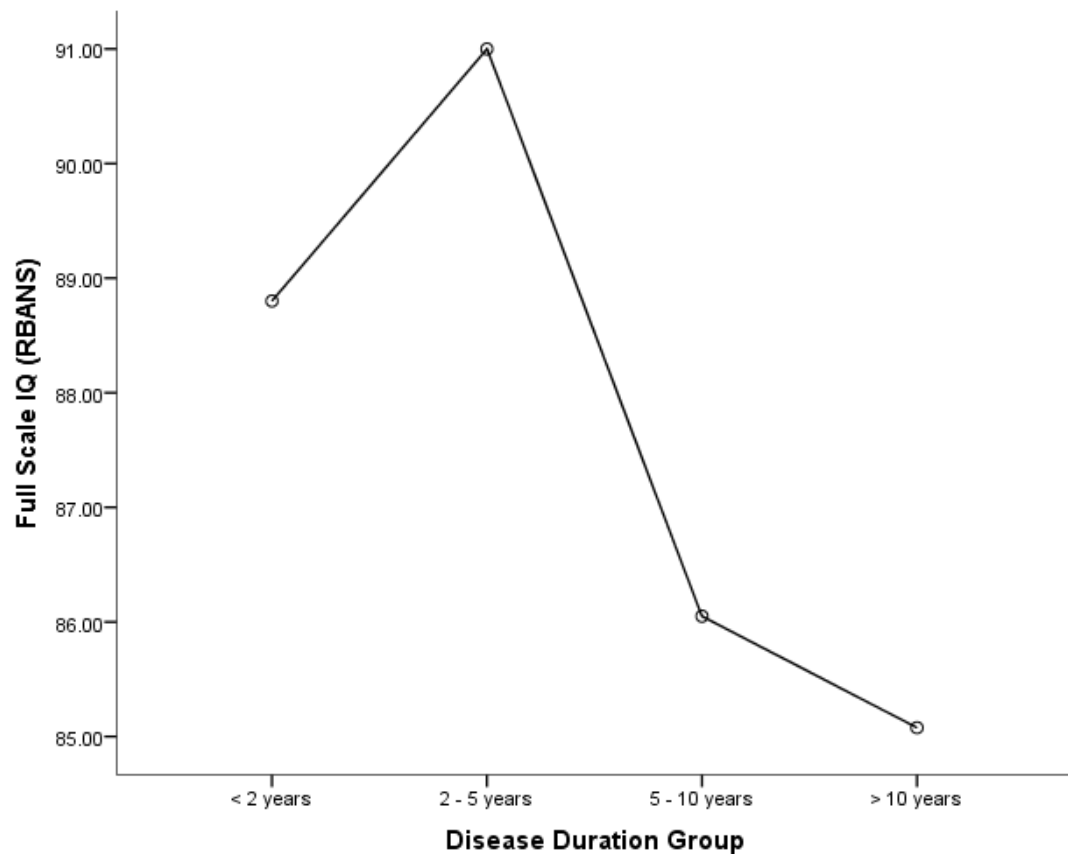


Figure 7. RBANS total scores by duration group

Examination of the means and standard error terms of the various groups led to the decision to merge the less than two and two to five year groups (1 and 2 in figures above). LEQ age group was also added to the analysis as a covariate. The result of this analysis demonstrate a significant relationship ($F(3,82) = 2.864, p = 0.042, \eta^2 = 0.095$) with the mean RBANS total score decreasing as disease duration increased.

Analysis of disease duration with NART FSIQ scores demonstrated no significant relationship ($F(30,54) = 1.297, p = 0.200$). This indicates that the pre-morbid IQ score is not affected by the progression of the disease, which is an indication that the NART is indeed not affected by Parkinson's Disease and hence is a reliable measure of pre-morbid IQ in the Parkinson's Disease population.

7.4 Discussion

7.4.1 *Life Experiences*

Overall participation in life activities measured by the Lifetime of Experiences Questionnaire (LEQ) did not demonstrate a relationship with decline in the Parkinson's Disease population. This is in contradiction to hypothesis four which predicted that there would be a relationship among these variables based on previous research in the Alzheimer's Disease population. However, deeper examination of individual types of life activity demonstrated that there were some relationships between particular activities and decline. The most consistent relationship that had the effect of reducing decline was with the playing of musical instruments across the various life stages. Playing an instrument at a regularity of monthly or more in either the young adult or mid-life stages demonstrated a reduction in overall cognitive decline and higher outcomes on both attention and language measures administered post decline. Attention, being one of the cognitive domains that are typically associated with decline in Parkinson's Disease, is likely the most significant of these. Though the relationships were not present in the later life stage, there were too few participants in the older age group that actually played an instrument on a regular basis for this relationship to be statistically significant; only two of the forty six participants over the age of 65 played an instrument on a monthly basis. The presence of this relationship warrants further investigation in a more evenly divided sample of musicians and non-musicians.

Playing a musical instrument is particularly interesting, both because it has been identified in previous literature, such as Zatorre et al. (2007), as being associated with the basal ganglia, and because it has a potential therapeutic application in the Parkinson's Disease population. The presence of the relationship with lower levels of decline at both

the young adult and mid-life stages suggests that it is not important when in life an instrument is taken up but rather just the act of regularly playing that contributes to a reduction in decline. This would be strengthened by further investigation demonstrating that the relationship also exists at the late life stage. The implication, then, is that people with Parkinson's Disease could potentially take up playing an instrument on a monthly basis as part of their treatment program and that this may offer them some protection against deterioration; particularly in the domains of attention and language.

Other factors that demonstrated relationships with overall decline are more difficult to control, but may be used as indicators to predict performance for individuals with Parkinson's Disease. While travelling at the young adult stage of life and undertaking further study at the mid-life stage demonstrated some indication of a protective relationship with decline, further analysis proved these relationships to be insignificant. Nevertheless, it is reasonable to assume that both of these factors are affected by both socio-economic status and cognitive ability at the life stages that they are associated with. Given the result of study one that indicated that individuals with more to lose tend to lose more, and these relationships indicate that those with more to lose tend to lose less, there is potential that this relationship is being obscured by variation in starting position. In any case, neither of these factors are useful in any more than a predictive context; there is not the opportunity for someone, once diagnosed with Parkinson's Disease, to increase their study or travel at a previous life stage.

Time spent with family at the late life stage also demonstrated a strong protective relationship with both overall decline and executive function results measured by the Brixton Spatial Anticipation Test. However, it should be noted that nearly all participants in the older age group indicated that they had daily contact with their family, the highest frequency that can be chosen on the LEQ. There was, then, a lack of distribution across the

various groups and the analysis is sensitive to outlier results in the low membership group. It should also be considered that this relationship may be equally influenced in the other direction; it may be that individuals with less cognitive decline are more able to make regular contact with their family and hence do so more rather than that spending time with their family has the effect of reducing the decline that they experience as a result of the disease.

There were a small number of other lifestyle factors that were associated with elevated cognitive decline. Participation in moderate level sport at the mid-life stage was one factor that demonstrated a relationship in increasing overall cognitive decline. This is in contrast to the anticipated result stated in hypothesis 5; physical activity was thought to potentially be useful in maintaining cognitive performance post diagnosis. However, the finding that physical exercise was related to increased cognitive decline held only for the early mid-life stage dataset, and was not found in late-life. There is the potential that a tendency for individuals to over report participation in socially desirable activities, particularly physical activities, has affected the data that this result is based on. Similarly to travel and study, this factor is not something that is within the control of the individual to change once the diagnosis of Parkinson's Disease is present and hence it only has utility as a predictive measure rather than having therapeutic application.

Another factor that demonstrated a significant relationship to increasing cognitive decline was participation in artistic activities at the late life stage. Increased decline in the information processing index (adjusted for motor speed) was found among the group reporting artistic activity in late life. An analysis run between late life art participation and motor speed per se demonstrated no significant relationship, hence this result is not likely influenced by art participants maintaining higher motor speeds and hence having their procession speed scores adjusted down on this measure. Unlike mid-life sport

participation, it is possible for individuals with Parkinson's Disease to make the choice to stop participation in art activities at the late stage of life in order to attempt to preserve their information processing function. While this result seems unintuitive, it is theoretically possible that by taking part in a particular activity, such as art, that utilises a particular part of the brain causes preservation of these areas of the brain at the expense of other functions in disease progression.

It should be considered that the multiple levels of analyses used to investigate these LEQ factor relationships may have increased the chance of type I errors being responsible for the relationships that are demonstrated. However, the effect size for the instrument result was large at both the young adult and mid-life stages, and the relationship between art participation and motor speed at the late life stage had a medium effect size.

7.4.2 Age

In accordance with hypothesis 1 age demonstrated a relationship with overall decline, with older participants demonstrating a larger change in cognition. However, this relationship was not significant in a simple analysis of age against decline, but rather required grouping of participants to demonstrate a relationship. LEQ age sections were used for this grouping, and with no participants in the young adult group this meant that participants fell into two age brackets, one group under 65 and one 65 and over. This grouping demonstrated a dramatic difference in decline, with the older group demonstrating more than double the decline percentage of the younger group on average.

Cognition is known to change as an individual ages, and this is seen particularly in populations experiencing degenerative dementias. It is not surprising, then, that given the degenerative nature of Parkinson's Disease and its effects on cognition, that the older age

group would demonstrate a greater overall decline than their younger counterparts.

Nevertheless, this is a good check for validity amongst the data; with this result being as expected and generally indicative of the known disease process it is more likely that other results in the study are valid findings.

The other contribution of this finding is to identify age grouping as a covariate that should be included in other analyses of decline in this population. This methodology was applied to study one after this finding in study two, and, while not as important for the LEQ measurements which are at life stages for an individual anyway, was taken into consideration for other analyses in this study.

7.4.3 Sex

Interestingly, overall decline was found to be greater for males than females. As the literature review reports, females tend to incur less deterioration across a number of disease processes including Alzheimer's Disease and deficits post traumatic brain injury, and this protection may extend to the Parkinson's Disease population (de Lau & Breteler, 2006). A possible explanation that has been postulated in previous research is that oestrogen acts as a protective mechanism against cognitive deterioration (de Lau & Breteler, 2006). It should be noted that the initial investigation did not demonstrate a significant relationship until age group was included as a covariate in the study.

Further analysis of sex effects with RBANS total and NART scores further supported the validity of this finding. RBANS total score was found to be an average of more than 8 points lower for males than females, while there was not a significant relationship demonstrated between sex and NART FSIQ scores. This indicates that although there is a difference between the sexes post-diagnosis or with disease progression there was not

already a split in the groups present before disease onset, and hence it follows that the difference is a result of the disease progression affecting the sexes differently.

It should be noted that mean NART score for the female group, while not significantly different to the male group, is slightly higher. Given the result of study one indicating that individuals with higher starting points tend to lose more, this makes the lower average decline for the female group from a slightly higher starting point stand out more in contrast to the overall pattern of decline.

7.4.4 Disease Duration

In contradiction to hypothesis 2, disease duration did not demonstrate a relationship with overall decline. Parkinson's Disease is a degenerative condition and hence it was anticipated that there would be a relationship in the time of disease progression and the amount of cognitive decline experienced by the individual. Interestingly, there was a relationship demonstrated between disease duration and RBANS total, though the direction of this relationship was unclear from the data. Grouping of participants into durations of less than 5 years, 5 to 10 years and 10 years or more appeared to indicate that RBANS Total score reduced as disease duration increased; as would be anticipated in a degenerative condition. However, the relationship demonstrated in this analysis was not statistically significant hence may simply be a quirk of the data collected rather than a reliable result. Similar effects were identified for WAIS digit span and FAS semantic fluency scores, but their direction was equally uninterpretable.

An explanation of why these disease duration results may not demonstrate the degenerative process is the methodology of measuring disease duration as time since diagnosis. Many individuals with Parkinson's Disease report, in retrospect, that their symptoms may have begun months, sometimes years before a formal diagnosis was made.

Most individuals are diagnosed after the onset of motor symptoms, namely a resting tremor. However research suggests that some symptoms, such as cognitive deficits or mood symptoms, may pre-date the onset of motor symptoms by several years. Due to the error variance in ascertaining actual disease duration (from first potential symptom) the disease duration in this study is measured from formal diagnosis. If, then, the point of diagnosis is thought of as the point at which a person with PD reaches a particular level of functional interference rather than the point of onset of the disease it is conceivable that an amount of cognitive decline has occurred up to this point that is outside of the disease duration as measured by this process. That is, two individuals with different starting IQs may already have declined to a similar point at the time of diagnosis and hence a flat relationship would be demonstrated between decline and duration post diagnosis.

An alternative explanation is that the relationship may be masked by other processes occurring for individuals in the study population. There exist many varying factors in Parkinson's Disease such as the cluster of symptoms a person presents with, time from onset of symptoms to symptom treatment and what type of medication an individual is taking. Similarly, as an individual gets older it becomes progressively more difficult to tease apart those cognitive symptoms attributable to Parkinson's Disease from those attributable to other potential dementing processes such as Alzheimer's Disease and cognitive deficits from small vessel ischemia which can lead to vascular type dementias. It is also important to examine the role mood disorders such as anxiety and depression can contribute to the overall cognitive presentation as both are known to cause cognitive deficits in the own right as well as compound the already existing deficits that may be occurring as a result of Parkinson's Disease degeneration. Study 3 will endeavour to examine the impact both depression and anxiety can have on cognition in Parkinson's Disease to better understand the contributions these are making to this and other relationships.

7.5 Limitations

Similarly to study one, the design of the decline measurement as a comparison between two separate measures that focus on a similar construct is less reliable than that which would be achieved in a longitudinal study using the same measures. While every effort was taken to ensure the accuracy of decline measurements, including confirmatory analyses with overall performance post disease rather than relying on decline alone and a demonstration of the lack of interaction between the factor and the individual's starting point, it must be noted that there is some error potential in the use of different measures to obtain pre and post scores.

The overall strength of the study's most useful finding, that playing musical instruments potentially contributes to protection against cognitive decline in Parkinson's Disease, was limited by the lack of participants who played a musical instrument in the late life stage. Further analysis in a group of elderly people with Parkinson's Disease who play musical instruments would be useful in determining whether this is a useful therapeutic aid. A study could even be constructed using a repeatable measure of cognition, such as the RBANS, for people with PD who played instruments and a control group who did not and their cognition be measured at a series of intervals to determine whether the music group did indeed experience less decline.

As discussed, the measurement of disease duration based on diagnosis is troublesome because it relies on the individual reaching a threshold level of functioning to be diagnosed rather than giving a true indication of the time at which the disease progress began. However, there is a lack of other options in terms of determining disease onset by another mean due to the current limitations of Parkinson's Disease diagnosis. Future understanding of the disease may lead to a test that can be performed on an individual to determine who will contract the disease or at what point the disease began to take effect,

and these may provide a measure of disease duration which, in turn, may demonstrate a relationship with cognitive decline.

Chapter 8: Study Three - Mood and Cognition in Parkinson's Disease

8.1 Aim and Hypotheses

The effects of mood disorders such as anxiety and depression on cognition are well documented. Performance on cognitive assessment tasks is detrimentally affected in individuals experiencing such mood disorders. Anxiety and depression both occur commonly with Parkinson's Disease, either organically or as a reactive process to disease progression.

This study aims to examine whether mood disorders affect overall decline in cognitive performance for individuals with Parkinson's Disease and whether this affects particular aspects of cognitive performance in this population.

Based on previous research it is hypothesised that:

1. A large number of sample participants will experience anxiety, depression or both at moderate to high levels.
2. Individuals experiencing anxiety or depression will have worse performance on cognitive measures including RBANS Total, BMIPB Adjusted, Brixton Spatial Anticipation Test, WIAS Digit Span and FAS Semantic Fluency measures.
3. Individuals with anxiety or depression will demonstrate a higher level of decline than their non-anxious / non-depressed counterparts.
4. NART FSIQ scores will not be affected by levels of depression and anxiety.

8.2 Methodology

8.2.1 Participants

This study was investigated using data collected from the same research group as in studies one and two. For information on participants in the study please see study one (section 6.2.1).

8.2.2 Selection of Measures

The rationale for the selection of the cognitive measures chosen for this study is the same as has been stated in study one (section 6.2.2).

8.2.3 Materials

The following materials were summarised in study one (section 6.2.2) and are described in more detail there.

- *The National Adult Reading Test (NART; Nelson & Willison, 1991)*
- *Repeatable Battery for the Assessment of Neuropsychological Status (RBANS; Randolph, 1998)*
- *Wechsler Adult Intelligence Scale, 3rd ed, Digit Span Subtest. (WAIS-III Digit Span; Wechsler, 2002)*
- *The Brixton Spatial Anticipation Test (Brixton; Burgess & Shallice, 1996)*
- *Birt Adult Memory and Information Processing Battery (BMIPB - Information Processing Task A; Coughlan, Oddy & Crawford, 2007)*
- *FAS Test of Verbal Fluency (Benton & Hamsher, 1989)*

The Hospital Anxiety and Depression Scale (HADS; Snaith & Zigmond, 1994):

The HADS is a 14 item ordinal scale that is used in clinical non-psychiatric populations to measure levels of anxiety and depression on two separate scales via the use of one dichotomous scale. This measure is used most in clinical populations as it examines few somatic symptoms that can co occur in psychiatric illnesses such as fatigue, insomnia and hypersomnia.

8.2.4 Procedure

The battery of neuropsychological assessments was administered as per study one (section 6.2.4).

8.2.5 Design and Analysis

An additional variable, cognitive decline, was calculated from the instrument results collected in the study. This variable was used to indicate change in cognitive function from pre-morbid to current functioning. This variable was calculated by subtracting current IQ level (as measured by the RBANS) from pre-morbid IQ level (NART IQ) and dividing the result by the pre-morbid IQ and multiplying by 100 to give decline as a percentage of original function. For example an individual with a NART score of 125 and a RBANS score of 100 would have a cognitive decline score of $(125 - 100) / 125 * 100$ or 20% decline. This decline measure was used as to examine change of cognition in further analyses in this study.

The NART-TriSplit variable was created to split the sample as evenly as possible into groups representing different levels of pre-morbid functioning. These groups represented NART scores of < 102, 102 – 112, and > 112, resulting in three groupings of 29, 28 and 28 participants respectively.

8.2.6 *Anxiety*

Mean anxiety score was examined across the sample as a whole and for each of the NART Tri Split groups to determine the overall level of anxiety in participants and to determine whether there was a relationship between pre-morbid IQ and the level of anxiety experienced by an individual.

One way analyses of variance were used to examine the relationship between anxiety and each of RBANS Total Score, each of the RBANS index scores, NART FSIQ, Brixton Spatial Anticipation Test, FAS Semantic Fluency Test, WAIS Digit Span and BIRT Memory and Information Processing Battery adjusted scores. In each case, anxiety total score was used as the independent variable and the other measure was used as the dependent variable.

In order to make effects clearer, these analyses were repeated with individuals placed into groups based on their anxiety scores. These groups were low (<8), mild (8-10), moderate (11-15) and severe (16+) anxiety and were based on the thresholds specified in use of the HADS questionnaire.

Cognitive decline was compared with anxiety total as measured by the Hospital Anxiety and Depression Scale (HADS). This analysis was conducted as a one way analysis of variance with anxiety level as the independent variable and decline as the dependent variable. The relationship between anxiety and cognitive decline was further examined by calculating correlations between cognitive decline and each of the questions related to anxiety on the HADS questionnaire.

8.2.7 *Depression*

As with anxiety, one way analyses of variance were used to examine the relationship between depression and cognitive measures. Depression was used as the independent variables in analyses with RBANS Total score, RBANS index scores, NART FSIQ, WAIS Digit Span, Brixton Spatial Anticipation Test, FAS Semantic Fluency and BIRT Memory and Information Processing Battery adjusted scores.

In a similar fashion to the anxiety analysis, these effects were further examined by grouping participants based on their score on the HADS depression scale. Groupings of low (<8), mild (8-10), moderate (11-15) and severe (16+) depression were based on the clinical guidelines for the HADS.

The relationship between depression and cognitive decline was measured through a one way analysis of variance with HADS depression level as the independent variable and cognitive decline as the dependent variable. Due to the findings of study two, this analysis was performed with and without age group included as a covariate. This analysis was extended to examine correlations between each of the depression scores and cognitive decline.

8.3 Results

8.3.1 Anxiety

Mean HADS anxiety for the entire sample was 6.95 with a standard deviation of 3.85. This indicates that the average person with Parkinson's Disease was experiencing anxiety just below the cut off for a mild level (8). Analysis of the relationship between pre-morbid IQ groupings and anxiety levels did not demonstrate a significant relationship, but did demonstrate a trend ($F(2, 84) = 2.872, p = 0.062, \eta^2 = 0.065$). The means and standard deviations for each of the NART TriSplit groups are shown in Table 15.

Table 15
Mean HADS Anxiety Scores by NART TriSplit Group

NART Group	Mean Anxiety	Std Dev.
1 (<102)	7.93	3.89
2 (102 – 112)	7.40	4.37
3 (>112)	5.61	2.90

Means and standard deviations were also calculated for each of the anxiety questions on the HADS to examine whether there were any particular questions that people with Parkinson's Disease scored higher on. Scores are given a value of 0 to 3 on the questionnaire, with 0 representing no anxiety and 3 representing the highest anxiety response for the question. These are shown in Table 16.

Table 16
Mean Scores for each of the anxiety based questions on the HADS

Question	Mean	Std Dev
1	1.01	0.67
2	0.83	0.85
3	1.18	0.88
4	0.95	0.56
5	0.80	0.80
6	1.26	0.91
7	0.92	0.85

RBANS total score was analysed by anxiety level to see if there was an effect on scores based on an individual's anxiety. This analysis did not demonstrate a significant relationship between anxiety and RBANS total score ($F(16,67) = 0.837, p = 0.654$). HADS anxiety was then analysed against each of the RBANS Index scores to check for effects on particular indexes.

Univariate analyses of variance between RBANS total score and each of the anxiety based questions on the HADS did not demonstrate any significant relationships.

Table 17
RBANS Index Score Relationships with HADS Anxiety Level

Index	df	F	η^2	p
Immediate Memory	16,69	0.472	0.099	0.952
Visuospatial	16,68	0.686	0.122	0.798
Language	16,68	2.177	0.339	0.014*
Attention	16,68	0.585	0.121	0.884
Delayed Memory	16,69	0.860	0.166	0.615

Anxiety did not have a significant effect on scores on the BMIPB Adjusted index ($F(15,58) = 0.623, p = 0.836$), WAIS Digit Span ($F(16,69) = 0.587, p = 0.883$), Brixton Spatial Anticipation ($F(16,62) = 1.172, p = 0.315$) or FAS Semantic Fluency ($F(16,69) = 0.620, p = 0.857$).

Cognitive decline was analysed against total HADS Anxiety level, and this did not return a significant relationship ($F(16,67) = 0.573, p = 0.893$). Note that this was also analysed using a regression analysis with similar results that can be found in Table C.2 in Appendix C.

8.3.2 Depression

Across the sample mean HADS depression score was 5.38, with a standard deviation of 3.52 indicating that the average person with Parkinson's Disease was experiencing depression at a level below the clinical cut off for mild depression (8). The relationship between pre-morbid IQ group and depression levels was not significant ($F(2,82) = 1.834, p = 0.166$). Means for each of the pre-morbid IQ groups are shown in Table 18.

Table 18
Mean HADS Depression Scores by NART TriSplit Group

NART Group	Mean Depression	Std Dev.
1 (<102)	5.70	3.68
2 (102 – 112)	5.97	3.26
3 (>112)	4.32	3.51

Means and standard deviations for each of the depression based questions on the HADS are given in Table 19. Similarly to the anxiety questions, these are calculated on a

score of 0 to 3 with 0 representing no depression and 3 representing the highest possible depression for that question.

Table 19
Mean scores for depression based questions on the HADS.

Question	Mean	Std Dev
1	0.82	0.76
2	0.52	0.70
3	0.45	0.61
4	1.74	0.89
5	0.78	0.85
6	0.78	0.91
7	0.36	0.72

Similarly to anxiety, depression relationships were measured through an analysis of variance with RBANS total scores to examine whether depression levels could be affecting the reporting of cognitive symptoms for relationship. HADS depression demonstrated a significant relationship with RBANS total ($F(14,69) = 2.285, p = 0.012, \eta^2 = 0.317$). The direction of this relationship is illustrated in Figure 8.

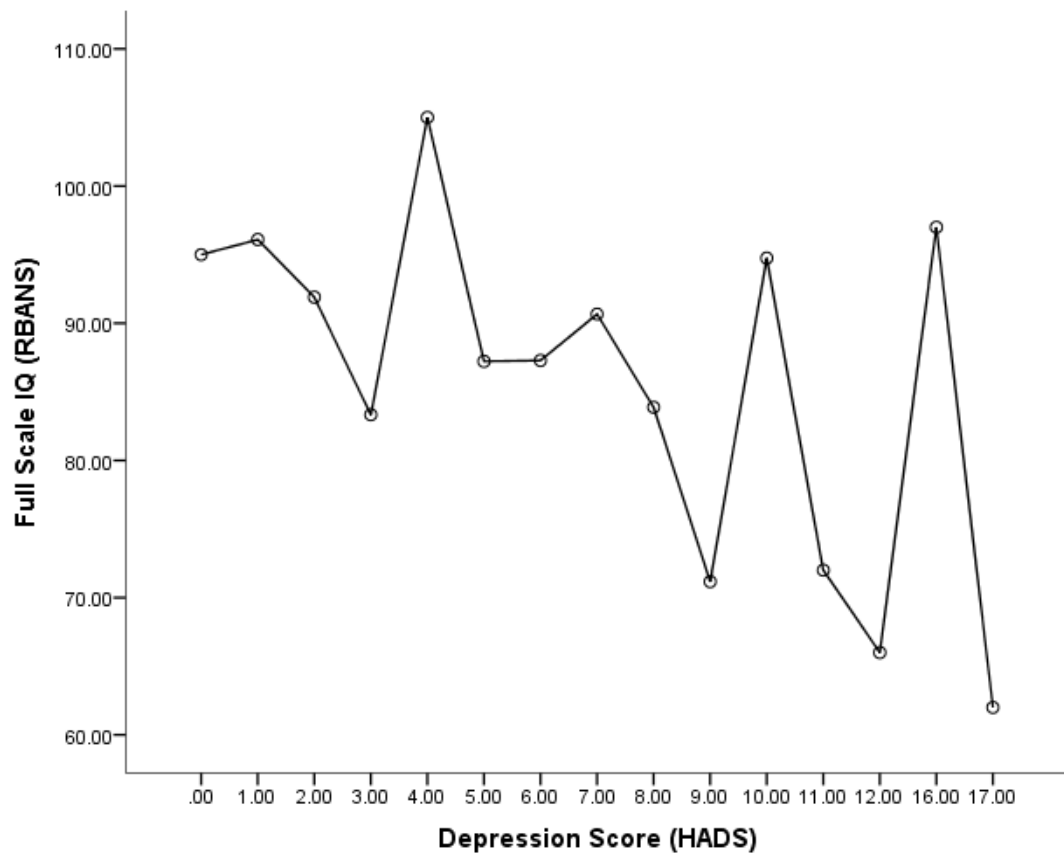


Figure 8. HADS Depression relationship with RBANS Total (mean)

These results indicate an inverse relationship between depression and cognition measured by RBANS; RBANS scores were highest for those participants with the lowest depression scores, and vice versa.

Further, each of the depression based questions on the HADS were analysed separately against RBANS total, with significant relationships demonstrate for questions 1 (“I still enjoy the things I used to”) ($F(3,78) = 3.095, p = 0.032, \eta^2 = 0.154$), 3 (“I feel cheerful”) ($F(2,79) = 5.065, p = 0.009, \eta^2 = 0.114$) and 7 (“I can enjoy a good tv or radio program or book”) ($F(2,79) = 3.546, p = 0.034, \eta^2 = 0.082$). In all cases higher depression scores were paired with a lower performance on the RBANS Total measure.

Additional analyses of variance were performed to determine relationships between HADS depression level and RBANS index scores. The results of these analyses are given in Table 20.

Table 20
RBANS Index scores relationship with HADS Depression

Index	df	<i>F</i>	η^2	<i>p</i>
Immediate Memory	14,71	1.186	0.189	0.305
Visuospatial	14,70	1.116	0.182	0.360
Language	14,70	2.533	0.336	0.005*
Attention	14,70	2.314	0.316	0.011*
Delayed Memory	14,71	1.533	0.232	0.122

Examination of the table indicates that higher depression scores were associated with lower scores on the RBANS attention and language indices. However, depression did not have a significant relationship with scores on the FAS Semantic Fluency Test ($F(14,71) = 1.253, p = 0.259$), the BMIPB Adjusted index ($F(14,59) = 1.087, p = 0.388$), the WAIS Digit Span test ($F(14,71) = 1.309, p = 0.224$) or the Brixton Spatial Anticipation test ($F(14,64) = 1.086, p = 0.387$).

HADS depression was also analysed against the cognitive decline measure, returning a significant relationship ($F(14,69) = 2.477, p = 0.007, \eta^2 = 0.334$). Analysis of the associated means plot (Figure 9) indicates that higher depression score is paired with greater cognitive decline. Note that this factor was also analysed using a regression analysis with similar results that can be found in Table C.2 in Appendix C.

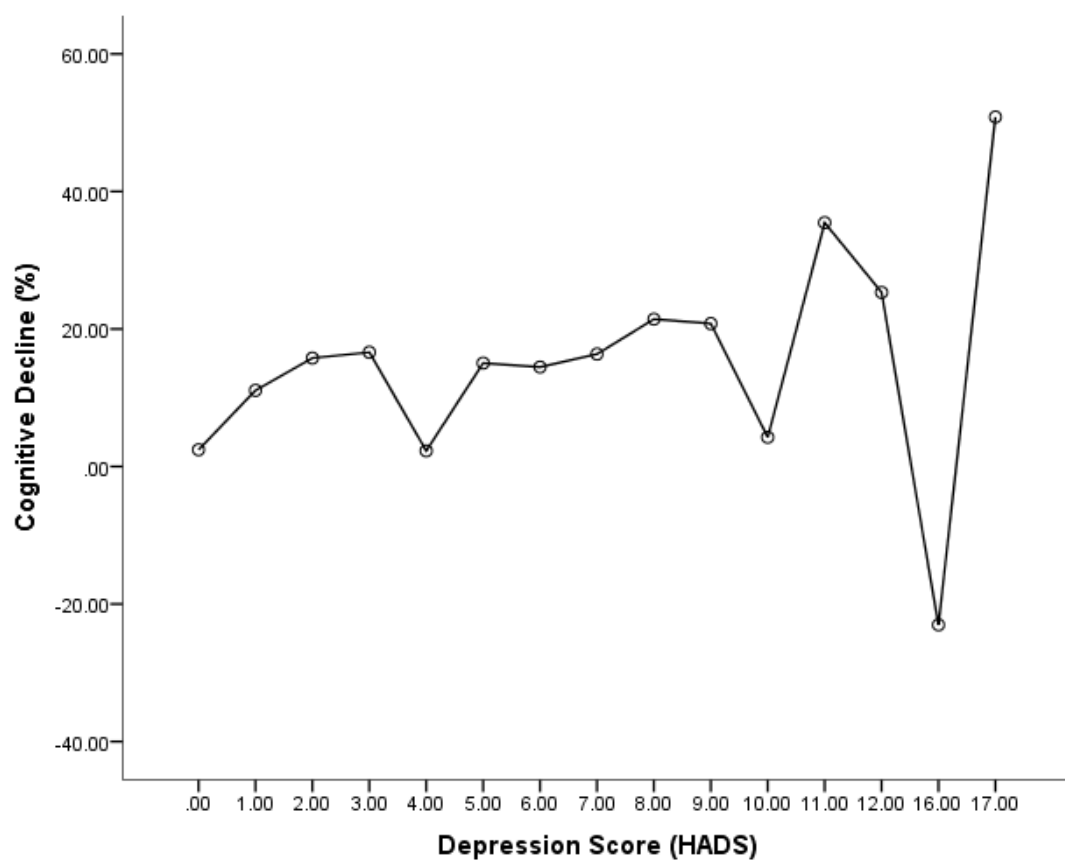


Figure 9. HADS Depression and Cognitive Decline

8.4 Discussion

Neither anxiety nor depression was present at a clinically mild or higher level on average across the study population. While anxiety and depression are often discussed as being present concomitantly with the disease, this result does not support that trend. It should be considered that there is considerable conjecture about the efficacy of measures of anxiety and depression accurately detecting these disorders in the PD population. This could lead to either or both of depression and anxiety being under reported in this result.

Pre-morbid IQ did not demonstrate significant relationships with either anxiety or depression. However, a strong trend was demonstrated between pre-morbid IQ and anxiety. Examination of the means demonstrated that individuals with higher pre-morbid IQ experienced lower levels of anxiety. A similar effect can be observed in the means for depression, though this relationship is weaker based on the analyses performed. While these relationships are not statistically significant, they provide some possible indicator of outcomes for an individual with PD in terms of their likeliness to experience a mood disorder as part of the disease and of that mood disorder's severity; particularly in regard to anxiety. Further investigation of this relationship may have implications for approaches to treatment in the PD population.

As anticipated in hypothesis 2, anxiety and depression levels were both associated with reduced performance on cognitive testing. While anxiety did not demonstrate a significant relationship with overall cognitive function performance, as measured by the RBANS, there was a significant reduction seen in performance on the language index. Depression was significantly related to reduction in performance on overall cognitive scores and further was shown to significantly reduce scores on both the language and attention indexes. Reduction in cognitive test performance has been associated with both

anxiety and depression, and these results demonstrate that this relationship is also present in the PD population meaning that there is advantage in treating mood disorders in the population.

The fact that both anxiety and depression demonstrate a relationship with score reduction on the language index is interesting because it is an area of function that is not typically associated with decline in PD. Indeed, this could imply that those individuals who do demonstrate lower levels of language ability with PD are in fact experiencing this decline as a result of a mood disorder rather than the disease itself and should receive treatment for the mood disorder to improve their language function. Interestingly, there was no significant relationship demonstrated between performance on the FAS semantic fluency task and either anxiety or depression. The FAS semantic fluency score correlates strongly with the language index in the normal population, and hence it could be anticipated that the effects seen between depression, anxiety and the language index would be reflected in the outcomes on the FAS. The FAS semantic fluency test concentrates on the ability to generate words given a condition that must be met, e.g. words beginning with the letter f. Given the nature of the impediments in task initiation associated with PD, it is likely that performance on this task is impaired across the PD population, and hence there may be little relationship demonstrated with anxiety or depression. That is, if all people with PD experience a level of impediment on this measure it is less likely to demonstrate differences between participants based on their level of anxiety or depression.

The relationship between depression and reduction in performance on attention based tasks, unlike the relationship seen with language, is indicative of a worsening in performance on an affected function for individuals with PD. Whether this is indicative of a reduced ability to adapt to modified function because of depression or a negative attitude reducing performance on testing, treating the depression in affected individuals with PD

may help to ameliorate the effects of their reduced attention abilities on their ability to perform activities of daily living.

Change in cognitive function, measured by the derived variable cognitive decline, was also demonstrated to have a significant relationship with depression and not with anxiety. At first glance this could be considered to be reflective of the relationship with performance on overall cognitive function, i.e. the reduction in overall performance of cognitive tasks due to depression exaggerates the difference of pre-morbid and current functioning. However, in combination with the fact that individuals with higher pre-morbid IQ experience lower levels of depression, it can be seen that this result may be due to under-reporting the effects of depression on cognitive decline. The results of study one that suggest that individuals with higher pre-morbid IQ tend to experience more measurable decline as a result of PD lend weight to this hypothesis.

It is interesting to note that despite the overall higher level of anxiety in the sample population it is depression that demonstrates a greater effect on cognitive outcomes. This is particularly relevant in terms of the relationship with attention scores which are already impaired in the PD population. The incidence of depression has been found to be under diagnosed in the PD population due to the overlap between PD and depression symptoms, with researchers estimating that around 50% of people with PD experience depression at a clinical level (Ravina et al., 2007). Given this, the effects of depression on cognition in the population suggest that depression should not be ignored in treatment of individuals with PD. Further research into this relationship may provide significant implications to treatment planning in PD.

While some aspects of hypothesis 2 were supported by the effects on RBANS total and index scores, other tests of semantic fluency, attention, executive function and processing that were administered did not demonstrate relationships with anxiety or

depression. This result is unexpected as both depression and anxiety have been demonstrated to negatively impact performance on cognitive tasks. One possible explanation for this discrepancy is that the masking effect of symptom overlap between PD and the measured mood disorders leads to under diagnosis of anxiety and depression in the population. This may, in turn, reduce the accuracy of the results to the point where a statistically significant relationship cannot be demonstrated. Alternatively, the discrepancy may be explained by the fact that the performance on these tasks is so impeded by the presence of the degenerative aspects of the disease that the effect of anxiety and depression is masked in the population. If either case explains this discrepancy then treating mood disorders might be unlikely to significantly improve performance on these tasks.

Examination of the average scores for each question of the HADS did not demonstrate any statistically interesting relationships. It is interesting to note, however that the highest average scoring question on the anxiety section was “I feel restless as though I have to be on the move” and the highest average scoring question on the depression section was “I feel as if I am slowed down”. Both of these questions can be related to movements on the person’s part, and each is affected by a physical symptom of PD; the anxiety question by the presence of tremors and the depression question by difficulties in initiation. These mood based questions that relate back to physical symptomatology may be causing an over-reporting of the levels of anxiety and depression in the sample. Further investigation into the validity of the HADS as a measure in the PD population may clarify the effect that the presence of these questions has in this population.

8.5 Limitations

This study shares a limitation with studies one and two in terms of the calculation of cognitive decline being based on a comparison of two different measures rather than as a result of a longitudinal study. This limits the study's ability to examine decline over specific areas of cognition and is only indicative of a change in function rather than a true measure of it. This is discussed further in the grand discussion.

As noted, overlap between PD symptoms and symptoms of anxiety and depression make the diagnosis of these conditions difficult in the PD population. The HADS is a short form questionnaire designed for speed of administration in a clinical setting that has demonstrated strong sensitivity and specificity, however there is some inherent risk that the overlap between PD symptoms influences the outcomes of this scale. This is highlighted in the relationship between the questions that had highest average scores and the known symptoms of PD.

There are a large number of statistical analyses performed to determine the results of this study and that can increase the incidence of type I errors in determining relationships. However, the relationships that are demonstrated and commented on fall into the large category on Cohen's effect size scale, and hence the likelihood of the relationships being due to type I errors is reduced.

Chapter 9: General Discussion

The overall goal of the present research was to test whether common measures of “cognitive reserve” would mediate against cognitive decline in a Parkinson’s Disease (PD) population. A secondary goal was to establish whether anxiety and depression influenced the cognitive functioning within the population.

Study 1 found that premorbid-IQ, a commonly used index of cognitive reserve, did not appear to have any protective influence on cognitive decline in a PD population. In fact the opposite was true; people with higher premorbid IQ had a greater decline. This finding, contrary to the hypotheses of the study and much previous research in cortical dementias, is likely explained in terms of Wilder’s law of initial values in which those who have more of “something-to-lose” show the greatest decline to a common level. It is notable that unlike previous research in which the cognitive reserve theory is supported, the current study used an ipsative approach to measuring cognitive decline, not an approach based on thresholds of impairment. The present finding agrees well with Pai and Chan (2001) who found an inverse relationship between cognitive decline and education in a PD population. The authors attributed the variation to individuals with higher levels of education being more sensitive to decline than their counterparts. This appears to be a very similar explanation to that offered in the current study; that people with “more of something to lose” are more vulnerable to dramatic loss than those with less to lose.

Study 2 examined the possibility that cognitive reserved indexed via rich lifetime activities would help protect against cognitive decline in a Parkinson’s Disease population. Again, contrary to hypotheses, no consistent relationship was found. Instead, just one factor (playing a musical instrument) appeared to potentially be associated with protection of cognition against disease pathology. Playing an instrument at a regularity of monthly or

more at various life stages was associated with higher levels of functioning on both the language and attention RBANS scores. This finding may be interesting for two reasons. First, it was the only lifestyle factor or index of cognitive reserve found to have any protective effect on cognition. Second, playing a musical instrument may have some potential practical and clinical application for disease treatment. Playing a musical instrument regularly is something that can be taken up by a person post diagnosis whereas traditional cognitive reserve factors like education and pre-morbid IQ cannot, of course, be changed by the person at a later time. There is a paucity of research available around the effects of lifestyle factors on cognitive performance, and this extends to the influence of playing a musical instrument. Further research in this area may help to prove or disprove the presence of this relationship.

Study 3 found that anxiety and depression were commonly found in a PD population and both were associated with poorer scores on cognitive tests. Depression, in particular, demonstrated a relationship with both language and attention outcome scores and a significant relationship with the level of overall decline. The relationship indicated by this result may have important implications for both treatment and research; in terms of treatment it identifies the necessity of treating mood disorders to improve outcomes for people with PD and in terms of research it identifies the necessity of allowing for the effects of mood disorders when conducting research into the PD population. These are emphasised by the conjecture in research around the accuracy of detecting mood disorders in PD and the apparent under-diagnosis that occurs as a result. Further research into the accurate diagnosis of mood disorders in PD would allow for a better understanding of their incidence and to allow researchers to more accurately control for the effects of these concomitant conditions.

As a proviso to the above, the causative direction of the relationship between cognitive decline and mood disorders is worthy of further investigation. The current study demonstrated a relationship between levels of depression and anxiety and levels of overall cognitive decline. It is, however, possible that this relationship could be read the other way, i.e. that higher levels of decline imply a higher incidence of mood disorders, potentially due to a reduction in coping skills. The causative direction of this relationship is worthy of future research.

Interestingly, the indexes that demonstrated a relationship with playing a musical instrument were the same indexes affected by depression (language and attention) and anxiety (language). These two indexes were also most preserved in the Pai and Chan (2001) study that demonstrated similar cognitive reserve results. Hence, these seem to be the areas of functioning that are most variably affected in the course of PD. The relationship between playing an instrument and the incidence of anxiety and depression was not examined in this study, but may be of interest in future research.

In terms of personal outcomes, then, the points of interest identified in this study that may be worthy of consideration in future research are the use of musical instruments as a therapeutic tool, and the importance of treating mood disorders, particularly depression, in minimising the cognitive effects experienced by individuals with PD.

While no commonly used measures of cognitive reserve were reliably found to moderate cognitive decline in PDs in the present research (potentially due to limitations covered later in this section) there were individual differences in cognitive deficits in the current PD which could not solely be explained by age, disease duration or mood effects. This may imply that other factors exist that affect the progression of the disease which were not measured or detectable in the current studies.

9.1 Limitations and Considerations

In any research, there are factors that affect the outcome that are outside of the researcher's control. A number of such factors have been identified before and during the research, and allowed for where possible. The following considerations and limitations should be considered when reviewing the findings of this research.

9.1.1 *Participant Recruitment and Demographics*

Participants were invited to participate in the research which may have skewed the study population as it is possible that a certain demographic were interested in participating than others (i.e. those who work in the area, have conducted research before etc). Due to this it is possible that those of higher average intelligence may have chosen to participate in the research which may have led to inflation in the mean FSIQ of those participants.

Due to the high incidence of depression within the population it is conversely possible that NART scores may have been artificially deflated with research by Watt and O'Carroll (1999) suggesting that an increased level of depression is associated with an increase in NART error scores.

While the effect of motor speed impairment was allowed for in determining an individual's processing speed by utilising both TMT A and BMIPB Motor Processing Task it is difficult to entirely and effectively remove the effect that motor impairment has on task performance.

Due to the advanced age of participants, as is common with PD populations, many individuals had co-morbid conditions such as heart disease, diabetes and arthritis. While those with co-morbid neurological conditions such as a diagnosed Alzheimer's Disease or

previous stroke or TBI were eliminated from the study this was reliant on self-report and not all conditions were able to be accounted for.

9.1.2 Influence of Medication

A major limitation of the present study was inability to control for the effects of medication. Due to the physical ramifications of withholding dopaminergic medication (such as an increase in motor disturbance) participants were instructed to remain taking their medication as prescribed. However, the time of day that participants were tested varied, depending on convenience of appointment time and similarly the time at which participants took their medication varied from person to person. Because of this it was difficult to control for medication effects, in particular the decline in functioning that occurs when dopamine is decreasing as the next dose nears and the effects that people have immediately after taking their dose. It is clear in the literature that the time of day in which someone has taken their medication can impact upon cognitive and physical functioning. Similarly, however, not taking medication can have adverse effects in terms of cognition and physical symptoms. Many studies note the difficulty in catering for this and generally, participants are instructed to take their medications as per usual so as little disturbance occurs to their overall PD symptoms as possible.

Another factor difficult to control in the current study was whether or not participants were tested in an 'on' or 'off' motor state. An 'on' motor state occurs when the person is getting good effect from their medication and they are able to control their movement freely. An 'off' state occurs at times when a person is unable to initiate movements or to stop tremors. These states are affected by variations of medication levels in the blood and are a normal, and cyclical, experience for people with PD. Many authors note that cognitive performance can alter depending on which state an individual is in,

though Lyros, Messinis and Papathanasopolous (2008) indicated that these differences are only apparent for people with more progressed, dementia, symptoms. Due to scheduling participants' assessment at times that were convenient to them, the motor state of the participants could not be controlled. Additionally, 'on' and 'off' states may occur at different times of the day on a daily basis for participants making it difficult for people to predict when their 'on' and 'off' motor states may be. This makes the feasibility of controlling this aspect in research questionable.

9.1.3 *Difficulties in Measuring Cognitive Decline*

As discussed in study one, the method of calculating cognitive decline used in this research is less reliable than a calculation based on administering the same measure in a longitudinal methodology. The comparison of different instrument scores adds a level of uncertainty to the decline calculation, though the research available correlating the measurements of the instruments used indicates that their comparison should be acceptably accurate. Nevertheless, this does introduce a limitation in terms of assessing the decline of specific functions in the disease; while it is useful to compare current levels of functioning on say the attention index against pre-morbid levels of overall functioning it is less indicative of the nature of decline as a measure of pre-morbid attention would be. The expense and difficulty of conducting longitudinal methodology based studies is discussed briefly in study one, with factors such as the advanced age of participants and the difficulty of identifying individuals before they are diagnosed with the disease highlighted as key issues. The difficulties in accurate and consistent diagnosis of PD must be considered again here; if there were a way to more efficiently diagnose PD through a medical test rather than observation it would be possible to more readily identify individuals at earlier stages of the disease and hence get a more accurate picture of functioning before significant disease progression has taken place. The other method, in

terms of gathering a volume of pre-morbid data, is to conduct a large scale study examining cognitive function of a large section of the population and then conducting follow up studies with those individuals who develop the condition. The expense, both in terms of the materials, interviewers, etc., and in terms of time that this type of study would require to yield results make it infeasible.

Cross sectional studies such as this one, then, provide indicative results that can be further investigated via more robust, expensive and time consuming methodologies. In many cases results, such as those around playing an instrument or treating mood disorders, lead to practical applications with minimal risks of negative outcomes and hence results may be enough to form the basis of experimental treatment regimes. Longitudinal studies on the effects of these regimes, however, would be required to assess their value.

9.1.4 Disease Duration

Another confound in the PD literature is ascertaining disease duration. While the progression of cognitive decline in PD appears insidious in nature there is a lot of evidence suggestive that the cognitive effects of PD may precede diagnosis by several years. Additionally, the rate of decline differs amongst people with PD meaning that it is difficult to have everyone assessed at the same point of their disease. Again, this may be alleviated by identification of more reliable methods of PD diagnosis that are able to determine the presence of disease earlier in its progression.

9.1.5 Volume of Statistical Analyses

A large amount of data was collected for all three studies and this resulted in a large number of analyses being conducted to determine the relationships that were discussed in each section. Utilising a large number of statistical analyses has been

associated with an increase in type I errors, or false positives, and hence there should be reasonable doubt applied to all demonstrated relationships. Effect sizes for all of the discussed relationships fell into the medium or large effect size category, going some way to alleviating this concern. Nevertheless, the influence of the methodology used in reaching the conclusions should be considered when determining the strength of the results.

9.1.6 Length of Assessment

The length of the assessment may have had some impact on the results of the study, particularly around whichever subtest were administered later in the battery. The assessment took approximately 2 hours to complete and while all participants were offered a break throughout testing fatigue may have had an impact on tests taken later in the assessment. The order of the battery was not changed throughout the assessment either meaning that possible order effects may have occurred and that any effects caused by fatigue would have occurred on similar tests for all participants.

9.2 Future Directions

Future research into cognitive reserve in PD would benefit from using a larger sample size to see if the indicators of cognitive reserve that were present in this study population are present and identifiable in a larger PD population. Similarly, it would be useful to examine cognitive reserve in other sub-cortical diseases such as MS, HD and progressive supranuclear palsy to determine whether the effects found within this study can be generalised to other sub cortical diseases or whether they are specific to PD.

It would also be useful to examine whether cognitive reserve correlates with brain reserve with several studies suggesting that brain reserve can be identified via PET, SPECT

and MRI. This was not feasible in this study due to budget constraints and access to equipment. However the literature reviewed suggests that this is another area that may provide important information in predicting disease progression in the population.

Future research could isolate whether the effects noted in the present research are specific to the particular tests used in this research, or whether they also hold when a variety of other cognitive tests. This research would be valuable to clarify the current finding that anxiety and depression as measured by HADS were associated with RBANS language skills but not the related FAS semantic fluency test. The cognitive reserve literature in cortical disease processes varies considerably depending upon test type, so examining the cognitive reserve question in PD using a large range of cognitive tests may also provide useful information for guiding clinicians in test usage in PD. Further research could investigate whether people with PD benefit from increasing their social and occupational participation at the time of diagnosis, or whether increased activity at this stage has no minimal protective effect for cognition.

In order to overcome some of the difficulties in the calculation of cognitive decline, the data collected for this study could be used as a baseline point in a longitudinal study. The RBANS has two forms and as such is a repeatable assessment which means that it is suitable for re-use with the population if they could be re-tested after a period of time. This would allow a direct comparison of test scores, and the calculation of a test-by-test based decline score, allowing better visibility of those functions which are continuing to degrade as a part of the disease process. While this would not provide any greater clarity on the level of function prior to disease onset it would demonstrate whether decline is still occurring for the participants and at what rate it is occurring. Similar analyses could be run to those in this study with the newly calculated decline variables in order to assess which domains are sensitive to which factors.

The relationship between regularly playing a musical instrument and performing better on the language and attention tests in PD is a valuable area for further study. While the result was significant in the sample it was noted that there were only a relatively low number of participants in the study who had a background of regularly playing an instrument. Nevertheless, the result is interesting both because of its presence indicating some measure of cognitive reserve in the PD population and because of its possibility to be used as a treatment in the disease and not just a predictor of disease progression. There is a lack of research available about the effects that regularly playing an instrument has on cognition, and further investigation is required to determine whether this is a specific relationship with PD or whether the relationship between instruments and performance on these tasks is present throughout the general population. There is also a need to examine a group with a higher representation of musicians, particularly in the older age grouping; there was only one over 65 in the study who regularly played an instrument and hence there was not the opportunity for the relationship to be statistically significant in that age group. Another approach to this would be to conduct a study of non-musician people with PD with a baseline cognitive assessment and have them practice instruments regularly over a period before reassessment. Results of such a study could provide information about the validity of such treatment programs in reducing the cognitive effects of the disease.

Lastly it may be worthwhile investigating the strange result in Study 2 in which practice of artistic activity in late life was associated with reduced performance on cognitive processing speed tasks. This result seems anomalous, and there is a lack of research to help determine whether this is a spurious result, a genuine result specific to PD or is something that could occur in the wider population. There is value in conducting further research to investigate this odd finding.

Beyond the specific issues central to the current research, there are a series of issue for PD diagnosis which complicate any research into PD. The first is in the diagnosis of PD itself, and extends to the diagnosis of MCI and PDD. The diagnosis of PD is based on clinical examination of cardinal symptoms which overlap with other disorders and may not be the first to appear in disease progression. Thus identifying how long the disease has been present in any individual is not easy and may lead to difficulties for research based around the stage of the disease. Issues surrounding the diagnoses of MCI and PDD are discussed in chapter 3 and need not be recovered here. However, diagnostic methods have led to some questionable research outcomes, such as those highlighted in study one. In these studies using a threshold based diagnosis for impairment that doesn't take into account the individual's pre-morbid level of functioning can over-report impairment in lower IQ populations and under report impairment in higher IQ populations. An individual who had an impaired language score, for example, before disease onset, would contribute to the incidence of impairment in that group attributed to the disease. Likewise a high function individual who declined to a low average level of functioning would indicate no change in function for the high IQ group in a threshold based diagnostic approach. These types of research errors could be avoided with more accurate and defined diagnostic measures.

Secondly, the diagnosis of mood disorders within the PD population is not entirely reliable as evidenced by the number of studies stating difficulties in determining their incidence in the population. The measure used to determine anxiety and depression in this study, the HADS, is a widely used and well researched short form instrument that has been validated for use in the PD population. Nevertheless, the symptom overlap between PD and mood disorders makes the results of this instrument questionable. As discussed in study three, the most highly rated items on the questionnaire were those that shared overlap with the physical symptoms of PD, indicating that the mood disorders may be

overrepresented. However, subjectively it is possible to consider that when asking someone with PD if they feel slowed down, for example, they could also attribute it to their disease and underrate their result leading depression being undervalued. Whether it is over or underrated for a given individual or in general has implications for both research and treatment, particularly when relationships are demonstrated between mood disorders and cognition, both in the PD and general populations. Even if this is only used as a basis to control for the effect of mood disorders while researching other effects on cognition, accuracy of detection of mood disorders in the PD population is essential. As such, further research into the existing measures of anxiety and depression in the PD population, or the development of a new questionnaire specific to the population, would be of great value to future research into the condition.

9.3 Clinical Implications

It was the hope of this research that indicators of cognitive reserve would be found in the PD population to help clinicians to predict outcomes of cognitive degeneration and to allow them to tailor treatment regimes based on predicted loss of independence and support requirements. Unfortunately, the current research was unable to reliably identify any general lifestyle factors predictive of cognitive decline in PD. However, current results indicate that playing a musical instrument regularly, and minimising anxiety/depression both appear to protect somewhat against cognitive decline. The finding that individuals who play musical instruments regularly demonstrated higher language and attention scores than those who did not regularly play an instrument provides a basis for music based therapy in this population. By introducing regular sessions of playing instruments for people with PD it may be possible to improve or retain functioning in these areas that would otherwise degrade as a part of the disease. This is very much in accordance with the

‘use it or lose it’ therapies that have become popular in other degenerative diseases, such as Alzheimer’s Dementia, in recent times.

Both anxiety and depression also demonstrated an influence on cognitive performance and cognitive decline. Treatment of mood disorders in the PD population may thus help to improve or retain cognitive functions in the areas of language and, in the case of depression, attention. . It has been noted that the diagnosis of mood disorders within the population is difficult, and this may limit or reduce otherwise needed treatment. Nevertheless, such treatment could potentially be used to great effect within the PD population and it that would benefit from further research and treatment trials.

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Appendix A

Lifetime of Experiences Questionnaire

Appendix B

Data Analysis Output (CD)

Appendix C

Regression Analyses

Table C.1
Regression Coefficients for demographic variables effect on Cognitive Decline

Step	Variable	Standardised Coefficient	t-value (<i>p</i>)
1	Constant		-0.527 (0.600)
1	Age	0.195	1.724 (0.089)
1	Sex	-0.106	-0.964 (0.338)
1	Disease Duration	0.078	0.686 (0.495)

The fit of this model was assessed as $F(2,80) = 1.818$, $p = 0.151$.

Table C.2
Regression Coefficients for mood variables effect on Cognitive Decline

Step	Variable	Standardised Coefficient	t-value (<i>p</i>)
1	Constant		3.540 (0.001)
1	HADS Anxiety	-0.066	-0.512 (0.610)
1	HADS Depression	0.199	1.543 (0.127)

The fit of this model was assessed as $F(2,81) = 1.252$, $p = 0.291$.

Table C.3
Regression Coefficients for LEQ Young Adult variables effect on Cognitive Decline

Step	Variable	Standardised Coefficient	t-value (<i>p</i>)
1	Constant		0.427 (0.671)
1	Time with Family	0.019	0.159 (0.874)
1	Playing an Instrument	-0.284	-2.290 (0.025)
1	Art Activities	0.068	0.555 (0.581)
1	Mild Sport	-0.067	-0.552 (0.583)
1	Moderate Sport	0.056	0.360 (0.720)
1	Vigorous Sport	-0.009	-0.061 (0.952)
1	Reading	0.105	0.854 (0.396)
1	Speaking a second language	0.114	0.895 (0.374)

The fit of this model was assessed as $F(8,67) = 0.828$, $p = 0.581$.

Table C.4
Regression Coefficients for LEQ Mid Life variables effect on Cognitive Decline

Step	Variable	Standardised Coefficient	t-value (<i>p</i>)
1	Constant		-0.261 (0.795)
1	Time with Family	0.041	0.274 (0.785)
1	Playing an Instrument	-0.299	-2.486 (0.015)
1	Art Activities	0.134	1.133 (0.261)
1	Mild Sport	-0.149	-0.986 (0.328)
1	Moderate Sport	0.389	2.785 (0.007)
1	Vigorous Sport	.0.175	-1.260 (0.212)
1	Reading	0.118	1.055 (0.295)
1	Speaking a second language	0.088	0.749 (0.457)

The fit of this model was assessed as $F(8,66) = 2.027$, $p = 0.057$.

Table C.5

Regression Coefficients for LEQ Late Life variables effect on Cognitive Decline

Step	Variable	Standardised Coefficient	t-value (p)
1	Constant		1.641 (0.109)
1	Time with Family	-0.257	-1.525 (0.135)
1	Playing an Instrument	-0.090	-0.565 (0.575)
1	Art Activities	-0.031	-0.192 (0.849)
1	Mild Sport	-0.088	-0.542 (0.591)
1	Moderate Sport	0.219	0.872 (0.389)
1	Vigorous Sport	0.076	0.314 (0.755)
1	Reading	0.058	0.361 (0.720)
1	Speaking a second language	-0.071	-0.453 (0.653)

The fit of this model was assessed as $F(8,40) = 0.563$, $p = 0.720$.

Based on the outcomes of the above models, 3 step regressions were performed at each of the LEQ life stages with demographic factors at step 1, mood factors at step 2 and LEQ factors at step 3.

Table C.6
Three Step Regression Coefficients for LEQ Young Adult variables effect on Cognitive Decline

Step	Variable	Standardised Coefficient	t-value (<i>p</i>)
1	Constant		-0.357 (0.722)
1	Age	0.165	1.280 (0.205)
1	Disease Duration	0.055	0.427 (0.671)
1	Sex	-0.052	-0.407 (0.686)
2	HADS Anxiety	-0.080	-0.539 (0.592)
2	HADS Depression	0.128	0.846 (0.401)
3	Time with Family	0.023	0.188 (0.851)
3	Playing an Instrument	-0.259	-2.028 (0.047)
3	Art Activities	0.064	0.502 (0.617)
3	Mild Sport	-0.082	-0.655 (0.515)
3	Moderate Sport	0.072	0.457 (0.650)
3	Vigorous Sport	-0.011	-0.068 (0.946)
3	Reading	0.080	0.637 (0.527)
3	Speaking a second language	0.143	1.072 (0.288)

The fit of this model was assessed as $F(13,62) = 0.840$, $p = 0.618$.

Table C.7
Three Step Regression Coefficients for LEQ Mid Life variables effect on Cognitive Decline

Step	Variable	Standardised Coefficient	t-value (<i>p</i>)
1	Constant		-0.199 (0.843)
1	Age	0.190	1.566 (0.122)
1	Disease Duration	0.046	0.370 (0.712)
1	Sex	-0.056	-0.460 (0.647)
2	HADS Anxiety	0.010	0.070 (0.944)
2	HADS Depression	0.038	0.252 (0.802)
3	Time with Family	0.009	0.057 (0.955)
3	Playing an Instrument	-0.269	-2.239 (0.029)
3	Art Activities	0.131	1.079 (0.285)
3	Mild Sport	-0.151	-0.918 (0.362)
3	Moderate Sport	0.378	2.607 (0.011)
3	Vigorous Sport	-0.175	-1.185 (0.241)
3	Reading	0.089	0.765 (0.447)
3	Speaking a second language	0.081	-0.666 (0.508)

The fit of this model was assessed as $F(13,61) = 1.524$, $p = 0.135$.

Table C.8
Three Step Regression Coefficients for LEQ Late Life variables effect on Cognitive Decline

Step	Variable	Standardised Coefficient	t-value (<i>p</i>)
1	Constant		0.411 (0.683)
1	Age	0.300	1.582 (0.123)
1	Disease Duration	0.077	0.427 (0.672)
1	Sex	-0.024	-0.139 (0.890)
2	HADS Anxiety	-0.113	-0.498 (0.622)
2	HADS Depression	0.011	0.046 (0.964)
3	Time with Family	-0.170	-0.898 (0.375)
3	Playing an Instrument	-0.089	-0.538 (0.594)
3	Art Activities	-0.062	-0.383 (0.704)
3	Mild Sport	-0.153	-0.918 (0.365)
3	Moderate Sport	0.208	0.754 (0.456)
3	Vigorous Sport	0.100	0.389 (0.700)
3	Reading	0.029	0.175 (0.862)
3	Speaking a second language	-0.113	-0.676 (0.504)

The fit of this model was assessed as $F(13,35) = 0.795$, $p = 0.660$.