Investigating the effects of motor symptom presentation on the development and assessment of non-motor symptoms in idiopathic Parkinson’s disease

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This thesis is submitted as partial requirement for the degree of Doctor of Psychology (Clinical) at the University of Tasmania, 2014
Declarations

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Acknowledgments

For my dad...

I would first like to acknowledge the support, guidance, and supervision received from Associate Professor Clive Skilbeck and Dr. Toby Croft. This research was made possible by the provision of funds and facilities by the Neuropsychology lab in the School of Psychology at the University of Tasmania, the Wicking Dementia Research and Education Centre, the Royal Hobart Hospital, and the Community Rehabilitation Unit (CRU). I would like to acknowledge the generosity of the individuals and their carers who agreed to participate. I would also like to thank Alison, Penny, Ticia, Liz, Brad, and Caroline for their assistance, and Brad, Pip, Dave, Kieran, and Michael for their less formal support and glasses of wine. Lastly, thank you to my Mum, Nan, and sisters, Sarah and Amy, for their enduring belief in my ability to achieve this goal.
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Investigating the effects of motor symptom presentation on the development and assessment of non-motor symptoms in idiopathic Parkinson’s disease

Leesa Green BA (Hons)
ABSTRACT

Parkinson’s disease (PD) is a degenerative sub-cortical neurological disorder primarily involving morphologic and neurochemical changes in the human brain, particularly the basal ganglia. Basal ganglia is a term used to identify areas of the basal forebrain and midbrain known to be involved in the control of movement and some higher cortical functions. Cardinal motor symptoms in PD include muscle rigidity, tremor, bradykinesia, a loss of postural reflexes and, in extreme cases, akinesia. These symptoms can be experienced either unilaterally or bilaterally. Non-motor symptoms in PD include cognitive decline, depression, sleep disturbances, hallucinations, and apathy. Changes in cognitive functioning in PD can range from mild cognitive impairment to Parkinson's disease dementia (PDD). While studies investigating a potential relationship between motor symptom phenotype and cognitive decline in PD exist, results have been equivocal to date. Additional research has been recommended and this was the aim of the current studies. Participants (n = 88) were recruited from the Royal Hobart Hospital and administered a comprehensive assessment battery that included demographic and mood measures, a range of cognitive measures covering immediate and delayed memory, executive functioning, visuospatial functioning, and language, as well as several tests of motor functioning. Study One examined the link between current motor functioning and cognitive performance. Despite no significant between groups differences on demographic variables such as age, years
of education, pre-morbid cognitive functioning, mood, and disease duration, participants in the lower motor functioning group consistently performed more poorly on all cognitive tasks included in the assessment battery. Study Two examined the impact of side of motor symptom onset, comparing the current cognitive functioning of participants who experience left sided, right sided, or bilateral motor symptoms at time of initial diagnosis. While no significant differences were found between those with left sided and right sided motor symptom onset, those with bilateral motor symptom onset were significantly ($p < .001$) more likely to achieve the poorest cognitive results. Study Three examined the potentially confounding impact of motor functioning and side of onset when assessing anxiety and depression in a PD population using the two-factor Hospital Anxiety and Depression Scale (HADS) as well as a three-factor model of the HADS that separated anxiety, depression, and psychomotor symptoms. Results cautioned against reliance on the traditional HADS for detecting mood symptoms in people with PD. Overall results indicate that motor symptom presentation can provide valuable information regarding cognitive functioning and mood in PD populations.
CHAPTER ONE

An Introduction to Parkinson’s Disease

First described in James Parkinson’s 1817 monography, ‘An essay in the shaking palsy’, and later termed Parkinson’s disease (maladie de Parkinson’s) by French neurologist Jean-Martin Charcot, this degenerative sub-cortical neurological disorder is characterised by a large number of motor and non-motor features. These features have the capacity to impact on an individual’s functioning to varying degrees (Jankovic, 2008). No definitive diagnostic test exists for Parkinson’s disease (PD), with the disorder typically being identified using clinical criteria. The development of PD symptoms is generally believed to be the result of damage to the cells of the pars compacta region of the substantia nigra (SNpc), which in turn stops producing the melanin containing neurotransmitter, dopamine (DA). When the DA levels in the substantia nigra decrease to a critical level, typically when the affected individual is around 60 or 70 years of age, motor and other symptoms of PD become manifest (Banich, 1997).

A national review undertaken by Access Economics (2011) reported that over 64000 Australians are living with PD (52% male, 48% female). This figure equates to over 850 per 100000 people over the age of 50. With the ageing of the population it is expected that the overall number of people diagnosed with PD will rapidly increase in the coming decades.

1.1 Aetiology

A number of aetiological factors have been investigated for their causative
potential in the development of PD. Despite the reporting of some single gene variant cases of PD, these diagnoses are rare and the vast majority of incidences are sporadic in nature. Late-onset, idiopathic (having no known cause) PD is typically thought to results from a combination of ageing, exposure to environmental toxins, and genetic risk factors (Chinta et al., 2013).

1.1.1 Age

PD is typically diagnosed from late middle age, with a marked increase in diagnosis during late age (Zigmond & Burke, 2002). This pattern is suggestive of a potential aetiological link between PD and ageing. This has been further supported by studies showing negative correlations between age and both striatal DA loss (Kish, Shannak, Rajput, Deck, & Hornykiewicz, 1997) and DA cell levels in the SNpc. However, Kish et al., (1997) concluded that the regional and subregional pattern of DA loss in normal ageing differs markedly from that detected in people with idiopathic PD. This indicates idiopathic PD cannot primarily be an age-related neurodegenerative process; however it does remain as a significant risk factor, a finding which has been well supported in subsequent reviews (Chinta et al., 2013; Zigmond & Burke, 2002).

1.1.2 Environmental Factors

Exposure to environmental toxins has been linked to the development of a number of diseases including cancers and neurodegenerative disorders like PD. Chronic exposure to the common herbicide, paraquat, as well as the heroin analogue, MPTP (methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine), have been identified as important specific risk factors for PD (Chinta et al., 2013). Additional studies have
shown associations between living in rural areas, the drinking of well-water, and/or herbicide/pesticide exposure, and the development of PD (Zigmond & Burke, 2002).

1.1.3 Genetics

Twin studies conducted in the 1980s indicated low concordance rates for PD among identical twins. Ward et al. (1983), with a participant pool of 65 monozygotic and dizygotic twins, found that only one set had definite concordance. Despite this, it has been recognised that PD can occasionally be identified in families, with the identification of specific, disease-causing genetic mutations. The most widely investigated genetic causes are \( \alpha \)-synuclein (see Chapter Two of this review for more detailed information), and parkin, a ubiquitin ligase protein (Trempe et al., 2013).

Mutations in the parkin gene have been shown to cause autosomal-recessive juvenile type parkinsonism that has an extremely early age of onset (as young as nine, with a mean age of 28; Ishikawa & Tsuji, 1996), and a symptom profile that differs quite significantly from idiopathic PD (Zigmond & Burke, 2002). The leucine-rich repeat kinase 2 (LRRK2) gene has also been investigated; however its prevalence is low and research has been largely inconclusive (Fritsch et al., 2012).

As mentioned, single gene variants of PD are extremely rare and the more likely cause is a complex interaction between genes that operate to increase or decrease PD susceptibility (Fritsch et al., 2012). Age and environment-related factors may then work to further modulate the underlying cause and type of PD.
1.2 Pathophysiology

The basal ganglia are a group of interconnected sub-cortical nuclei that span the telencephalon, the diencephalon and the midbrain (Albin, Young, & Penney, 1989) and are known to be involved in the control of movement (Fitzgerald, Greuner, & Mtui, 2007). The primary afferent structure of the basal ganglia is the striatum, which itself is divided into the putamen and the caudate, and its primary output structures are the substantia nigra pars reticulata (SNpr) and the medial globus pallidus (see Figure 1.1). The SNpc also projects and receives projections from the striatum, with the neurotransmitter of the SNpc being DA (Albin et al., 1989).

![Figure 1.1. Coronal section showing the basal ganglia in relation to surrounding structures (DeLong, 2000).](image)

Current theory suggests that there are four main DA pathways in the brain; the nigrostriatal pathway, which regulates movement, appears most obviously affected in people with PD, especially in the early stages of disease progression. As well as the nigrostriatal pathway, the additional pathways are the mesocortical, the
mesolimbic and the tuberoinfundibular pathway and it is likely that DA degradation along these non-striatal pathways is what causes the neuropsychiatric symptoms that can present in people with PD (Mandal, 2010; Zigmond & Burke, 2002).

The hallmark pathological feature of PD is the loss of DA neurons in the SNpc. During autopsy even those with only mildly progressed PD show approximately 60% dopamine degradation and it is this loss, in addition to possible dysfunction of the remaining neurons, which leads to a 70-80% reduction in DA levels in the corpus striatum (Albin et al., 1989; Zigmond & Burke, 2002). As mentioned, these neurons project to the striatum and their loss can lead to changes in the activity of the neural circuits within the basal ganglia that regulate movement. In essence, there appears to occur an inhibition of the direct pathway and an excitation of the indirect pathway (Mandal, 2010). The direct pathway facilitates movement and the indirect pathway inhibits it, thus a loss of these cells leads to increased inhibition of the ventral interior nucleus of the thalamus, which sends excitatory projections to the motor cortex. The resulting condition is hypokinesia or a hypokinetic movement disorder. Hypokinesia refers to progressive deterioration in the quality of continuous movements (Miller Koop, Hill, & Bronte-Stewart, 2013). This manifests as progressively reduced amplitude in handwriting, progressively reduced length of stride/gait when walking, and progressively reduced speed and amplitude in repetitive finger or limb movements. In addition to this, hypokinesia can also affect speech, causing a progressive reduction in speech volume.

Neurological deficits in PD occur when the availability of DA falls below the levels needed for rapid compensation. Additionally, while there are numerous groups of dopaminergic neurons in the central nervous system, it is the loss of DA neurons in the SNpc, and particularly its ventral-lateral tier, that accounts for all motor
symptoms in PD (Zigmond & Burke, 2002).

As mentioned above, significant DA degradation and cell loss typically occur prior to any outward manifestation of the disease (Zigmond & Burke, 2002). This delay in symptom onset is thought to be due to compensatory tactics such as increased DA synthesis by the remaining neurons, decreased DA clearance in the post synaptic cleft (Banich, 1997) and a degree of inherent redundancy in DA terminals and receptors that allows for maintenance of striatal function despite significant neuronal loss (Zigmond & Burke, 2002).

Although some dopaminergic neurons are spared in PD, such as those in the ventral tegmental area and the hypothalamic systems as well as those in the descending spinal dopaminergic systems, there is evidence to suggest that it is not only dopaminergic neurons that are lost. As degradation in dopaminergic neurons alone cannot account for the experience of cognitive decline in PD, additional research has suggested involvement by other areas of the brain (Banich, 1997). Other catecholaminergic neurons, as well as the serotoninergic neurons of the raphe nuclei and the cholinergic neurons of the nucleus basalis of Meynert, are also lost, which may partially explain the onset of cognitive decline (Zigmond & Burke, 2002).

An additional hallmark pathological feature of PD is the development of Lewy bodies (Zigmond & Burke, 2002). Lewy bodies are abnormal proteins (α-synuclein & ubiquitin) typically identified within the cell soma but also detected in neuritis or free in extracellular space (Dickson, Feany, Yen, Mattiace, & Davies, 1996). Current research suggests that the death of dopaminergic neurons by α-synuclein is caused by a defect in the process by which proteins are transported between two major cellular organelles, these being the endoplasmic reticulum and the golgi apparatus.
In people with PD, Lewy bodies are most commonly observed in those regions of the brain associated with neuron loss, including the subthalamic nucleus, locus coeruleus, the dorsal motor nucleus of the vagus and the nucleus basalis of Meynert. In addition to this, people with PD may also exhibit Lewy bodies in the spinal cord, the peripheral autonomic ganglia, the diencephalon and the neo-cortex (Dickson et al., 1996). Lewy bodies can be detected through histology of brain tissue.

Most recently, the role of the substantia innominata (SI) in the development of PD has been investigated with preliminary results suggesting a positive correlation between the thickness of the SI and scores on the Mini Mental State Exam, with Oikawa, Sasaki, Ehara, and Abe (2004) finding that the SI, within which the nucleus basalis of Meynert resides, appears atrophied on magnetic resonance imaging data in people with diagnosed idiopathic PD.

1.3 Motor Symptoms

The cardinal motor symptoms in PD are muscle rigidity, tremors, bradykinesia (motor slowing), a loss of postural reflexes and, in extreme cases, akinesia (lack of movement; Gazewood, Richards, & Clebak, 2013; Verreyt, Nys, & Santens, 2011). These symptoms can be experienced on both sides of the body (bilaterally); however it is also possible to have hemi-Parkinsonism where motor symptoms manifest unilaterally. In addition to this, it is important to note that motor symptoms do not manifest in the same way for all individuals (Gazewood, Richards and Clebak, 2013).

Tremors usually appear as an oscillating movement and are more obvious when the muscles are at rest, meaning the affected limb or body part (this symptom
may also present in the jaw) trembles when not being used. Tremors are the most common of the motor symptoms, occurring in approximately 70% of all people diagnosed with PD (Hoehn & Yahr, 1967). Resting tremor is the typical PD tremor; however most people with tremor symptoms will also suffer a postural tremor (tremor during activity) which can be more disabling than resting tremor as it can hinder the performance of activities of daily living to a significant degree.

In the early stages of diagnosis it is important to distinguish postural tremor from essential tremor, as an isolated postural tremor is *clinically* identical to essential tremor. Only the presentation of additional parkinsonian features can separate the two, with essential tremor involving no neuropathology while PD related postural tremor will involve, among other things, DA deficiency and the presence of Lewy bodies. Additionally, PD postural tremor can be differentiated from essential tremor depending on the latency of the tremor emergence, with essential tremor emerging almost immediately following forearm extension, while PD postural tremor latency is typically seconds and can be as much as a minute (also known as re-emergent tremor; Jankovic, Schwartz, & Ondo, 1999).

The underlying biochemical defect causing both resting and postural tremors remains relatively unknown, with researchers postulating that tremor severity parallels homovanillic acid (HVA) reduction in the pallidum (Elsworth, Leahy, Roth, & Redmond, 1987). HVA is a major catecholamine metabolite and is associated with DA levels in the brain (Elsworth et al., 1987; Klauschen, Goldman, Meyer-Lindenberg, & Lundervold, 2009). Researchers have also indicated that the ventralis intermedius of the thalamus and the STN also play a role in the development of tremor in PD and both are key targets in surgical interventions (Rodriguez et al., 1998).
As previously mentioned, further research has used both humans and laboratory animals with parkinsonian symptoms brought about by exposure to the metabolised neurotoxin MPTP. However, while this neurotoxin selectively affects the nigrostriatal dopaminergic system in much the same way Parkinson’s disease does, people with MPTP poisoning typically exhibit a more pronounced postural tremor than the resting tremor seen in PD, making direct comparisons between the two disorders inherently problematic (Ballard, Tetrud, & Laneston, 1985; Snyder & D’Amato, 1986).

Rigidity, or increased muscle tone, refers to stiffness and inflexibility of the muscles. Typically, muscles stretch when moving and relax when at rest, in rigidity the muscle tone of an affected limb is always stiff and does not relax, resulting in decreased range of motion. Rigidity appears to be less variable than tremor and contributes to subjective reports of stiffness and tightness, at times causing discomfort and pain. Caution should be taken during differential diagnosis, as rigidity can mimic arthritis and bursitis. Arthritis refers to joint inflammation, while bursitis is inflammation or irritation of the bursa, a lubricating-fluid filled sac located between tissues such as tendons and bones. Rigidity in people with PD is often associated with postural deformities resulting in a flexed neck and trunk posture as well as flexed elbows and knees (Jankovich, 1987). While the neurophysiology of rigidity is poorly understood, it is believed that surgical lesions of the palladium or of the ventral lateral nucleus of the thalamus may alleviate this symptom (Fitzgerald et al., 2007).

Bradykinesia, or motor slowing, results from failure of the basal ganglia output nuclei to reinforce the cortical mechanisms that prepare and execute movement commands (Agostino et al., 2003). In addition to bradykinesia, a person
with PD is likely to have incomplete movements, difficulty initiating movements and a sudden stopping of on-going movements (freezing; Stocchi, 2009). The degree of bradykinesia and akinesia, like various other symptoms experienced by people with PD, appears dependant on the emotional state of the individual. Sudden surges in emotional energy can result in kinesia paradoxica, or the production of relatively normal speed motor reflexes such as those required when catching a ball (Jankovich, 1987). This phenomenon would seem to indicate that motor programs remain relatively intact in people with PD; however they experience difficulty accessing them without the aid of external triggers. When bradykinesia manifests in the oropharynx, it can lead to difficulties swallowing, which can in turn cause aspiration pneumonia which increases mortality significantly (Zigmond & Burke, 2002).

Another fundamental deficit experienced by people with PD is an inability to automatically execute learned sequential motor plans (Lezak, Howieson, & Loring, 2004). This impairment is believed to result from a disconnection between the basal ganglia and the supplementary motor area (SMA). The SMA is a region of the sensorimotor cerebral cortex and has not only been implicated in the planning of motor actions and bimanual control, but also in actions that are under internal control, such as the performance of a sequence of movements that have been memorised (Shima & Tanji, 1998). The basal ganglia projects to the SMA via the globus pallidus and the ventrolateral thalamus which in turn projects to the motor cortex (Marsden, 1982). Inadequate basal ganglia activation of the SMA is believed to result in the reduction of the pre-movement potential in people with PD.

Research into reaction time tasks further supports this theory, with Evarts, Teravainen, & Calne (1981) providing results suggesting both reaction time and
movement time are independently affected in those with PD, with people exhibiting bradykinesia tending to experience more specific impairment in choice reaction time tasks. Bradykinesia also correlates with the reduction of DA levels in the caudate nucleus. Further to this, Berardelli, Rothwell, Thompson, & Hallet (2001), postulated that the pathophysiology of bradykinesia involves a failure of basal ganglia output to reinforce cortical mechanisms that prepare and execute movement commands. They suggest this deficit is most apparent in midline motor areas and leads to particular difficulty with self-paced movements, prolonged reaction times and abnormal pre-movement electroencephalograph activity (Berardelli et al., 2001).

Additional clinical features of PD include a series of secondary motor symptoms such as the presence of hypomimia which is a reduction in facial expression, dysarthria or slurred speech, dysphagia or difficulty swallowing, and sialorrhea or the excessive secretion of saliva (Jankovic, 2008). Secondary motor symptoms can also include micrographia, or the production of abnormally small handwriting, shuffling gait, festination or an involuntary increase in gait speed, freezing, and the reappearance of the primitive glabellar reflex resulting in Myerson’s sign. The glabellar reflex is elicited via repetitive tapping on the forehead. Typically, individuals will blink following the first few taps only. Persistent blinking in response to taps is known as Myerson’s sign and is indicative of neurological dysfunction. Myerson’s sign is most commonly seen in Parkinson’s disease populations.

Dystonia, a neurological disorder in and of itself, may also present whereby the individual experiences sustained muscle contractions which in turn cause limb twisting and repetitive movements.

PD involves a number of sensory deficits that can also impact on motor
functioning to varying degrees (Konczak et al., 2009). These deficits include difficulties with tactile discrimination, weight, pain and visual depth perception, and kinaesthesia, or the awareness of body and limb position and motion in space (Konczak et al., 2009; Wright et al., 2010). While impairments in appendicular kinaesthesia have been well established within the PD population (Konczak et al., 2009; Konczak, Krawczewski, Tuite, & Maschke, 2007; Zia, Cody, & O’Boyle, 2002), more recently, impairments in axial kinaesthesia have been shown to significantly impact upon the patient’s ability to stand, balance and walk safely (Wright, et al., 2010), and as having a significant influence on quality of life (Cano-de-la-Cuerda, Vela-Desojo, Miangolarra-Page, Macias-Macias, & Munoz-Hellin, 2010).

These motor symptoms have also been shown to be indicative of the type and severity of PD the patient can expect to experience. The divide is believed to be between those experiencing tremor as opposed to bradykinesia and rigidity, with tremor being suggestive of a more benign disease course (Lezak et al., 2004).

1.4 Non-Motor Symptoms

In addition to debilitating motor symptoms, people diagnosed with PD also face the possibility of developing a range of non-motor symptoms that can be equally debilitating.

1.4.1 Cognitive Decline

Changes in cognitive functioning in PD can range from mild cognitive impairment to Parkinson's disease dementia (PDD). Due to differences in diagnostic criteria, methodology, and participant characteristics, the suggested epidemiology of
PDD tends to vary significantly (Miereles & Massano, 2012). Some studies have suggested that as many as 78-90% of people with PD will develop some kind of cognitive impairment in addition to their motor disturbances (Emre, 2004; Poewe et al., 2008), while other studies have produced figures as low as 10% (Miereles & Massano, 2012).

Studies have also indicated that people with PDD have a unique clinical profile that differs from the neuropathology found in Alzheimer’s disease (Poewe et al., 2008) and is more consistent with Lewy-body dementia (Galvin, Pollack, & Morris, 2006). Typically, cognitive changes in PD manifest as impairments in attention, executive, and visuo-spatial functions, with memory encoding and language abnormalities playing a less significant role than they do in Alzheimer’s disease (Poewe et al., 2008). People with PD tend to exhibit symptoms of prefrontal dysfunction, such as difficulties initiating responses, difficulties with serial and temporal ordering and executive planning impairments (Freedman, 1990).

Due to the many ways in which PD can manifest in any given individual, it can often present the treating physician with diagnostic confusion and cause delay in the initiation of treatment plans (Jankovich, 1987). In its early stages, parkinsonian symptoms are easily confused with those that represent disorders such as Alzheimer’s disease, arthritis, bursitis, depression, stroke and even normal ageing.

As mentioned, people with PD can experience cognitive deficits that range from mild cognitive impairment (MCI) through to PD dementia. A recent review of the literature found that MCI is common in non-demented people with PD, with increasing age, motor symptom severity, and disease duration all combining to affect risk (Litvan et al., 2011). Definitions of what constitutes MCI in PD and its clinical correlates have remained significantly heterogeneous however, prompting the recent
development of universal diagnostic criteria by a commissioned taskforce (Dirnberger & Jahanshahi, 2013). The inclusion criteria, described by Litvan et al. (2012), state that the PD diagnosis must first be clinically established based on the UK PD Brain Bank criteria. Further to this they add cognitive deficits (as reported by the patient, a caregiver, or observed by the clinician) must be present on testing, and should not significantly interfere with functional independence. Exclusion criteria include the presence of parkinsonism other than idiopathic PD, a diagnosis of PD dementia, other plausible primary explanations for cognitive decline (eg. delirium, stroke, major depression etc), and other PD-associated comorbidities that may significantly influence cognitive testing (e.g., psychosis, severe motor impairments, fatigue etc; Litvan et al., 2012).

Typically, the earliest sign of cognitive compromise in people with PD is bradyphrenia, or slowness of thought, impaired attention and motivation, a lack of spontaneity, inflexibility, and forgetfulness (Lees, 1994). Although people with PD can usually arrive at the correct answer to a question or problem, they tend to do so slowly, needing to overcome a form of mental inertia (Banich, 1997). This gradual slowing can lead to poor performance across a number of tasks, particularly those requiring planning skills, and can also infiltrate other cognitive domains such as language production and visuospatial functioning. The motor symptoms experienced by people with PD can all impinge on their ability to perform cognitive tasks, particularly tasks with a heavy motor component such as verbal fluency, and articulation.

Secondly, people with PD can typically expect to experience memory deficits, particularly as the disease progresses (Aarsland & Kurz, 2010; Foltynie, Brayne, Robbins, & Barker, 2004). While long term memory for both verbal and
visuo-spatial material appears intact on recognition trials, people with PD often have difficulty recalling information (Banich, 1997). This pattern of memory loss suggests that the temporal lobes remain relatively intact in PD, while memory dependent upon the integrity of the frontal lobes is more adversely affected. Research also indicates that short term memory remains relatively spared in PD, although when a distractor task is included performance rapidly declines and it has been suggested that this is indicative of attentional deficits rather than pure memory degradation.

An additional cognitive domain affected by the onset of PD is executive functioning (Barone et al, 2011; Meireles & Massona, 2012). People with PD will typically exhibit deficits in planning, switching between categories (cognitive flexibility), sequencing, and problem solving or abstract thinking (Barone et al., 2011; Dalrymple, Kalders, Jones, & Watson, 1994).

1.4.2 Affective Disorders

Affective disorders in Parkinson’s disease can include apathy, psychosis, mania, impulse control disorders, DA dysregulation and DA agonist withdrawal syndromes, as well as anxiety and depression, some of which are inherent to the disease, while others are treatment side-effects (Aminian & Strafella, 2013).

Rates of depression in people with diagnosed PD are much higher than rates found in other long term degenerative disease and motor impaired populations, with research indicating clinical depression levels ranging anywhere from 2.7 to 70% (Burn, 2002). Possible explanations for this disparity include the use of different clinical tools and definitions to assess for the presence of depression, as well as sampling biases inherent in study populations (Burn, 2002), and the significant under-reporting of depression as a symptom of PD (Chaudhuri & Shapira, 2009). In
their review of the non-motor symptoms seen in PD, Chaudhuri and Shapira also indicated that the clinical definition of depression in PD is complicated and comprises features that may be indicative of early cognitive decline.

Likely exogenous causes of depression and apathy in PD include activity restriction and physical disability (Bogart, 2011). It is also possible that a neurobiological explanation exists for the increased rates of depression manifesting in the PD population. The pattern of depression in PD does not parallel the progression of motor symptoms, suggesting that it is an independent process that may affect particularly vulnerable people (Remy, Doder, Lees, Turjanski, & Brooks, 2005). Dysfunction of a combination of dopaminergic, serotonergic and noradrenergic pathways in the limbic system has been implicated in the development of depression in people with PD (Chaudhuri & Shapira, 2009). Early PD reviews (e.g., see Hoehn & Yahr, 1967) suggested that 70% of people with PD will present with tremor as their initial symptom, however, more recent reviews have shown that it is likely non-motor symptoms such as mood and sleep disturbances can present up to ten years prior to motor symptom onset (Chaudhuri & Shapira, 2009).

Remy and colleagues (2005) concluded that the development of depression in people with PD is associated with a specific loss of both DAergic and noradrenergic innervation in cortical and subcortical regions of the limbic system.

While there have been some attempts to use DA therapy as a treatment for depressive symptoms in PD, these studies have typically been small, non-randomised, and not placebo controlled, making their results difficult to generalise. In addition to this, a confounding factor of studies investing the anti-depressant potential of dopaminergic agonists such as pramipexole, pergolide, and ropinirol (Pahwa et al., 2007; Rektorova et al., 2003) is that these drugs have the added benefit
of improving motor symptoms. It is possible that this reduction in motor symptoms is what improves mood ratings, as opposed to the medication directly affecting mood itself.

Forty percent of people with PD will experience anxiety, with symptoms manifesting as generalised anxiety disorder, panic attacks, phobic disorders, obsessive compulsive disorder and other anxiety disorders (Aminian & Strafella, 2013; Leentjens et al., 2011). While there is some evidence to suggest a potential neurobiological basis for the presence of anxiety symptoms in PD (Aminian & Strafella, 2013; Blonder & Slevin, 2011), there are likely other factors at play also, including psychosocial factors and difficulties with accurate assessment due to overlap with the physical symptoms synonymous with PD (Leentjens et al., 2011).

1.4.3 Other Non-motor Symptoms

In addition to the debilitating motor and cognitive symptoms people with PD will experience, they are also likely to report hallucinations, sleep disturbances, and apathy (Khoo et al., 2013). In combination with cognitive decline, it is these non-motor symptoms that significantly impact quality of life as disease progresses (Martinez-Martin, Rodriguez-Blazquez, Kurtis, & Chaudhuri, 2011).

1.5 Risk Factors for Poorer Cognitive Outcomes

While a number of demographic and clinical factors have been investigated for their potential role in determining cognitive outcomes in PD, initial results were largely mixed and inconclusive (Aarsland & Kurs, 2010; Miereles & Massano, 2012). More recently studies have indicated the emergence of several possible key risk factors. Hobson and Meara (2004), in a longitudinal study involving people with
PD in the UK, found associations between the development of PD dementia and increasing age, later age of PD symptom onset, more severe parkinsonism, the presence of hallucinations, institutional care placement, the presence of depressive symptoms, the presence of memory and language impairment at baseline, and lower median levodopa (motor symptoms treatment medication) doses. This study also compared the individuals with PD to a control cohort assessed over the same four year period and found that individuals with PD were four times more likely to develop dementia than those in the control group. Of particular note, Hobson and Meara (2004) found the strongest neuropsychological predictor for the development of PD dementia to be poorer memory and language functioning at baseline assessment, while later age of onset, increasing disease severity, and the presence of hallucinations were the strongest demographic and clinical predictors of development of PD dementia. The identification of these predictors allows for better understanding of possible disease progression, and makes possible the implementation of interventions specific to the individual.

1.5.1 Motor Symptom Severity

A number of potential risk factors have been identified for cognitive decline in PD; however the severity of parkinsonism experienced by the person with PD has emerged as a potentially preponderant factor (Miereles & Massano, 2012). Levy et al. (2002), used a longitudinal design to investigate both age and motor symptom severity as potential risk factors, with results indicating that it is a combination of the two (increased age & more severe motor symptomatology) that increase risk, rather than either of the two factors alone. In contrast to this, Ebmeier et al. (1990), also using a longitudinal design, found that while severity of parkinsonism was predictive
of increased risk, age did not appear to be a significant factor.

A recent review of cognitive impairment in idiopathic PD concluded that while it is generally accepted that general motor symptom severity is predictive of cognitive decline, it is not clear whether it is associated with a particular motor symptom phenotype (Palavra, Naismith, & Lewis, 2013). The authors reported while that the majority of studies conclude non-tremor based motor features such as bradykinesia and rigidity are associated with cognitive decline, other studies that have found people with PD with a tremor-dominant motor phenotype experience more significant cognitive decline, while yet further studies have found no differences between the motor phenotypes (Palavra et al., 2013).

1.6 Implications of Diagnosis

PD is a progressive disorder, although rates of progression have been difficult to determine due to the effects of medications and surgical interventions, and they tend to vary significantly between symptoms (Vu, Nutt, & Holford, 2012). The most common sequence of limb involvement in PD is from one upper limb to the ipsilateral lower limb initially (typically within approximately one year), with the contra-lateral limbs then affected within three years (Fitzgerald et al., 2007). The patient may also exhibit rhythmic tremor of the lips and tongue, pronation-supination of the forearms and flexion-extension of the fingers.

Due to improvements in clinical diagnostic criteria and a significant increase in the information known about the disease, untreated PD is rare, with the use of medications markedly improving the individual’s quality of life. Current therapies target the motor symptoms that are characteristic of PD, and as a consequence the most debilitating aspect of the disease tends to be the symptoms outside the scope of
these medications. As the disease progresses, disability switches to those areas of motor symptom presentation which typically respond poorly to medications, such as swallowing and speech difficulties, as well as balance and gait disturbances.

The average life expectancy of an individual diagnosed with PD is somewhat reduced when compared to both age matched healthy controls and individuals diagnosed with other common diseases associated with older age (Willis et al., 2012). Dysphagia (swallowing difficulties), age, cognitive decline, and a more severe disease presentation are all indicative of increased mortality rates (Fritsch et al., 2012), with dysphagia in particular being linked to cases of aspiration pneumonia (Lin et al., 2012; Zigmond & Burke, 2002).

1.7 Current Treatments

At present there is no known cure for PD; however medications, surgical options and the interventions of multidisciplinary allied health teams can provide some relief from presenting symptoms. Choice of approach regarding the use of medications and surgical interventions is heavily dependent upon the symptom presentation manifest in the individual. Motor fluctuations and dyskinesias brought about by medication regimes should also be considered (Fritsch et al., 2012).

1.7.1 Drug Therapies

There are three main classes of drugs typically used in frontline management of PD; levodopa (L-DOPA), DA agonists, and catechol-O-methyltransferase or monoamine oxidase B inhibitors, with L-DOPA being the most widely used medication of the past thirty years (Freuen & Norton, 2008).

L-DOPA is metabolised into DA in the dopaminergic neurons by dopa-
decarboxylase. As motor symptoms develop in people with PD due to a lack of DA in the substantia nigra, the ingestion of L-DOPA and the subsequent increase in DA levels can temporarily ameliorate, or at least reduce, motor symptom presentation in some people with PD (Freuen & Norton, 2008). A downside to this route of L-DOPA administration is that approximately 5-10% of the L-DOPA passes through the blood brain barrier, with the remaining active ingredient metabolised into DA in other parts of the body (Freuen & Norton, 2008). This can result in a number of side effects, including nausea, dyskinesias, and stiffness.

In an attempt to halt the metabolism of L-DOPA in extraneous body regions, the peripheral dopa-decarboxylase inhibitors carbidopa and benserazide are typically added to L-DOPA based medications (i.e., the carbidopa/levodopa combination, Sinemet® and the benserazide/levodopa combination, Madopar®) (Pagonabarraga, 2010).

A significant downside to the use of artificial L-DOPA is that it eventually becomes counter-productive, with a significant reduction in the endogenous formation of L-DOPA taking place. Over time, prolonged use of this medication will result in the development of motor complications, dyskinesias and fluctuations in response to medications, leading to rapidly cycling symptom presentation (Fabbrini, Juncos, Mouradian, Seratti, & Chase, 1987; Fahn et al., 2004).

DA agonists have been shown to have a similar effect on symptoms as L-DOPA as they bind to the dopaminergic post-synaptic receptors. Initially used in people with PD displaying L-DOPA side effects to counteract the dyskenesias and rapid cycling of symptom presentation and response to medications, DA agonists are now more frequently used as front line medications, with the aim to delay motor complications (Pagonabarraga, 2010). As with L-DOPA, DA agonists also present a
set of significant, however not quite as severe, side effects, including hallucinations, insomnia, nausea and constipation (Freuen & Norton, 2008).

Finally, monoamine oxidase b (MAO-B) inhibitors can increase the levels of DA in the basal ganglia by blocking its metabolism. These medications work by inhibiting MAO-B, resulting in higher concentrations of DA in the striatum. As with DA agonists, MAO-B inhibitors can be used to delay the use of L-DOPA in early motor symptom presentation, however they are also less effective than L-DOPA (Pagonabarraga, 2010).

1.7.2 Surgical Interventions

When drug therapies are no longer providing adequate motor symptom relief doctors may consider surgical treatments. The surgical treatments have been developed following empiric observation of motor disturbances following brain lesions, and have led to techniques such as deep brain stimulation (DBS; Kopell & Greenburg, 2008), and neural grafting.

1.7.2.1 Deep Brain Stimulation (DBS)

DBS involves the surgical implantation of a brain pacemaker which sends high frequency electrical pulses (130-185 Hz) to targeted brain regions including the internal segment of the globus pallidus, the STN, and the pedunculopontine nucleus (Hedlund & Perlmann, 2012). The theory behind DBS postulates that paralysing the subthalamic nucleus neurons using high frequency stimulation via implanted electrodes disinhibits the locomotor centre (Fitzgerald et al., 2007). Treatment often results in significant improvements in motor functioning and activities of daily living (ADL) scores and anti-parkinsonian medication regimes can often be reduced.
following surgery (Hedlund & Perlmann, 2012).

Historically, DBS has been contraindicated in people with PD and co-morbid neuropsychiatric disorders and is typically only used in late stage disease progression and for people with PD who are intolerant to medications. However, more recent research carried out by Chopra et al. (2013) found no greater risk of adverse psychiatric event occurrence at six months post-DBS follow up and concluded DBS to be safe for people with PD and co-morbid psychiatric disorders.

1.7.2.2 Neural Grafting

Neural grafting involves the transplantation of foetal dopamine neurons into the striatum of people diagnosed with PD. The aim of this surgical approach is to re-establish normal DA networks that are capable of restoring feed-back controlled release of DA in the nigrostriatal system, thus alleviating the motor symptoms associated with PD (Hedlund & Perlmann, 2012). At present the feasibility of this approach is uncertain, with a number of key factors impacting success rates, including cell survival, the extent of reinnervation, and the ability of the transplanted cells to relieve L-DOPA related dyskinesias without causing “off medication” effects. Additionally, some people with PD have reported post-surgical increases in dyskinesia, indicating further research and understanding is required (Hedlund & Perlmann, 2012).

Unfortunately, all current therapeutic and surgical techniques centre on the more widely understood and easily treated motor symptoms manifest in PD. As yet, there is nothing available to reverse, halt or even delay the cognitive decline that people with PD can typically expect to experience. Allied health professionals can play a large role in aiding continued independence in this area with practical tools
and the provision of support networks.

Foetal substantia nigra grafts, gene therapy and the striatal infusion of growth factors are all currently being trialled as future treatment options (Fitzgerald et al., 2007).

1.8 Summary

Parkinson’s disease (PD) is a degenerative subcortical neurological disorder characterised by a large number of motor and non-motor features and primarily involving morphologic and neurochemical changes in the basal ganglia. Basal ganglia is a term used to identify areas of the basal forebrain and midbrain known to be involved in the control of movement and some higher cortical functions (Fitzgerald et al., 2007). Typical motor symptoms include unilateral or bilateral muscle rigidity, tremor, bradykinesia, a loss of postural reflexes and, in extreme cases, akinesia (Gazewood et al., 2013; Verreyt et al., 2011). Non-motor symptoms include cognitive decline, depression, sleep disturbances, hallucinations, and apathy (Khoo et al., 2013). Changes in cognitive functioning in PD can range from mild cognitive impairment to Parkinson's disease dementia (PDD). At present there is no known cure for PD and the choice of approach regarding the use of medications (for example, levodopa, dopamine agonists, & MOA-B inhibitors), surgical interventions such as deep brain stimulation, and allied health involvement is heavily dependent upon the symptom presentation manifest in the individual.
CHAPTER TWO

The Basal Ganglia and Parkinson’s Disease

As reviewed in Chapter One, Parkinson’s disease (PD) is a subcortical disorder primarily involving morphologic and neurochemical changes in the human brain, particularly the basal ganglia (Cools, 1984).

2.1 The Basal Ganglia

Basal ganglia is a term used to identify areas of the basal forebrain and midbrain known to be involved in the control of movement and some higher cortical functions (Fitzgerald et al., 2007). The five principal nuclei of the basal ganglia are the caudate and putamen, collectively known as the striatum, the globus pallidus, the substantia nigra, and the subthalamic nucleus (STN; see Figure 1.1).

Historically, it was believed that the basal ganglia were primarily involved in motor control, however recent evidence has emerged and an expanded role for the basal ganglia, including into areas of both motor and cognitive functioning has been suggested (Leisman, Melillo, & Carrick, 2013).

2.1.1 Striatum

The basal ganglia receive afferent input from the entire cerebral cortex and in particular the frontal lobes (Leisman et al., 2013). The primary afferent structure of the basal ganglia is the striatum (Albin et al, 1989; Tisch et al., 2004). The striatum is made up of three subdivisions, the caudate nucleus, the putamen, and the ventral striatum, which is made up of the nucleus accumbens and the olfactory tubercule.
The striatum is the major recipient of inputs to the basal ganglia from the cerebral cortex, thalamus and brain stem, with its neurons projecting to two morphologically similar output nuclei, the globus pallidus and the substantia nigra (DeLong, 2000).

Specific areas of the striatum receive excitatory, glutaminergic projections from all areas of the cortex (DeLong, 2000). In addition to this, the striatum also receives excitatory inputs from the thalamus, the midbrain (via dopaminergic projections), and the raphe nuclei (via serotonergic inputs).

The main cell type in the striatum is the gamma-aminobutyric acid (GABA)-ergic medium spiny projection neuron, with these cells being both major cortical input targets as well as the sole source of output (DeLong, 2000). In addition to these cells, the striatum also contains two inhibitory interneurons, both of which have extensive axon collaterals that reduce the activity of the output neurons. Despite being relatively few in number, these inhibitory interneurons are responsible for the majority of the tonic activity in the striatum (DeLong, 2000).

2.1.2 Globus Pallidus

The globus pallidus is divided into external (GPe) and internal (GPi) segments, and lies medial to the putamen (Fitzgerald et al., 2007; Tisch et al., 2004).

The GPe is a relatively large nucleus that receives projections from two major basal ganglia input nuclei, the substantia nigra pars compacta and the STN (both discussed below; Kita, 2007). In addition to this, the GPe sends its output to many basal ganglia nuclei, including the STN, striatum, GPi, and substantia nigra, making it a central component of the basal ganglia circuitry; in particular of the
indirect pathway that relays striatal input to the STN (Kita, 2007). The GPi is one of two output nuclei of the basal ganglia.

2.1.3 Substantia Nigra

As with the globus pallidus, the substantia nigra is comprised of two zones, the pars reticulata (SNpr), which is functionally related to the GPi, with both utilising GABA as their neurotransmitter, and the pars compacta (SNpc), made up predominantly of dopaminergic cells and neuromelanin (DeLong, 2000; Floor & Wetzel, 2002; Meiser, Weindl, & Hiller, 2013). Neuromelanin is a dark pigment derived from oxidised and polymerised dopamine (DA), and accumulates with age in large lysosomal granules in the cell bodies of dopaminergic neurons. It is neuromelanin which accounts for the dark discolouration of the SNpc (DeLong, 2000).

DA neurons in the substantia nigra are integral for the initiation of voluntary movements and also play a role in cognitive activities such as set shifting and habit learning (Floor & Wetzel, 2002). Once 80% of the DA neurons in the substantia nigra have been lost, motor symptoms indicative of PD manifest, while smaller losses of DA neurons seen in normal ageing and preclinical PD may also cause mild deficits such as slowed reaction times and reduced postural control.

In the SNpc, PD is characterised by a significant reduction in melanised cell numbers, indicative of massive degeneration of dopaminergic neurons, though the exact nature and extent of this degeneration remain uncertain (Floor & Wetzel, 2002).
2.1.4 Subthalamic Nucleus (STN)

The STN contains glutaminergic cells, the only excitatory projections of the basal ganglia and is located just below the thalamus. It is closely connected, anatomically, with both the globus pallidus and the substantia nigra (DeLong, 2000). The majority of the cortical afferents to the STN arise from the supplementary motor area (SMA), pre-SMA, and the dorsal and ventral pre-motor cortices. These projections innervate the dorsal aspect of the nucleus and are an integral component of the basal ganglia motor loop (Hamani, Saint-Cyr, Fraser, Kaplitt, & Lozano, 2004).

The STN plays a prominent role in the pathophysiology of parkinsonian symptoms and has become the optimal target for surgical interventions such as deep brain stimulation (Guridi & Obeso, 2000). It is estimated that between 30 and 50% of all STN neurons are related to movement, with most of the unit localised in the dorsal portion of the nucleus and activated by passive and/or active movements of single, contralateral joints (Hamani et al., 2004). In addition to this, 20% of the STN neurons are related to eye fixation, saccadic movements or visual stimuli. These neurons are located in the ventral region of the STN and are part of circuits that include the frontal eye fields, the caudate nucleus, the GPe, the SNpr. Activation of the STN drives SNpr activity, subsequently serving to inhibit the superior colliculus and thus enable the maintenance of eye position on an object or the recovery of fixation following saccade (Hamani et al., 2004).

STN activity in PD is characterised by several factors including augmented synchrony, a loss of specificity and an increase in receptive field sizes, with units responding not only to single contralateral joint movements, but to ipsilateral and
multiple joint movements also, and an increased firing rate to between 35 and 50 Hz (Hamani, 2004).

2.1.5 Summary

The basal ganglia are comprised of four principle nuclei, the striatum, the globus pallidus (GPe & GPi), the substantia nigra (SNpc & SNpr), and the STN, with the majority of these nuclei projecting exclusively to other nuclei within the basal ganglia; this has the effect of creating a subcortical network within the basal forebrain (Uttera & Bassoa, 2008). The SNpr and the GPi make up the two output nuclei of the basal ganglia, while the input nuclei include the striatum and, to a lesser extent, the STN (Uttera & Bassoa, 2008). The basal ganglia influence cortical control of voluntary movement by regulating the activity of the motor nuclei of the thalamus (Pollack, 2001). The GPi and the SNpr serve to innervate the thalamus, the superior colliculus and the pedunculopontine nucleus (PPN), with these regions in turn influencing a wide range of functions including: motor, sensory, and cognitive cortical information processing, movements of the head and eyes, spinal cord processing and aspects of locomotion (Uttera & Bassoa, 2008), as well as maintenance of posture, the completion of both voluntary and over-learned movements, the control of timing and switching between two or more motor acts, and in motor planning and learning (Banich, 1997). Add to this the fact that the input nuclei receive information from almost the entire cerebral cortex and it becomes clear that the basal ganglia play a key role in many neuronal and information processing systems.
2.2 Basal Ganglia Circuitry

Beginning in the cortex, there are at least four basic circuits that traverse the basal ganglia before returning to the cortex. These circuits are a motor loop, a prefrontal (cortical) loop, a limbic loop, and an oculomotor loop (Alexander & Crutcher, 1990; Fitzgerald et al., 2007; Gale, Amirnovin, Williams, Flaherty, & Eskandar, 2008).

These four basal ganglia-thalamocortical circuits all share certain features, for example, in each circuit, specific cortical areas send excitatory (or glutaminergic) projections on to the striatum (Alexander & Crutcher, 1990). Due to their high rates of spontaneous discharge, the GPi, SNpc and ventral pallidum exert a GABA-ergic inhibitory effect on their target nuclei in the thalamus. Within each of the four previously mentioned circuits, this inhibition appears to be differentially modulated by two opposing but parallel pathways, the ‘direct’ and ‘indirect’ pathways (Alexander & Crutcher, 1990). These efferent pathways have opposing effects on the basal ganglia output nuclei and, consequently, on the thalamic targets of these nuclei. Activation of the direct pathway disinhibits the thalamus and increases thalamocortical activity, while activation of the indirect pathway further inhibits the thalamocortical neurons. In summary, activation of the direct pathway will facilitate movement, while activation of the indirect pathway will inhibit it (DeLong, 2000).
Figure 2.1. Circuit diagram for the direct and indirect pathways in the basal ganglia (Leisman et al., 2013). Neurotransmitters: Glu, glutamate; Ach, acetylcholine; DA, dopamine; Enk, enkephalin; SP, substance P. Nuclei: GPe, external segment of the globus pallidus; GPi, internal segment of the globus pallidus; SNC, substantia nigra pars compacta; SNr, substantia nigra pars reticulate; STN, subthalamic nucleus; VL, ventral lateral nucleus; VA, ventral anterior nucleus.

Due to the parallel structure of these four circuits, the basal ganglia are capable of concurrent participation in a number of different functions, including cognitive, oculomotor, skeletomotor, and limbic (emotion processing & memory
formation) tasks (Alexander & Crutcher, 1990). The development of PD affects all four of these identified circuits in various ways.

2.2.1 The Motor Loop

The motor loop, primarily responsible for learned movements, and also involved in preparation for future movement (Alexander & Crutcher, 1990), begins in the sensorimotor cortex and is made up of two known pathways, the direct and the indirect (Fitzgerald et al., 2007; Pollack, 2001). These two opposing pathways connect the striatum to the SNpr and the GPi, the output nuclei of the basal ganglia. The direct pathway travels through the corpus striatum and the thalamus and is made up of striatal projection neurons which send an inhibitory GABA projection to the output nuclei (Fitzgerald et al., 2007; Pollack, 2001). The indirect pathway differs from the direct pathway in that it consists of a separate population of striatopallidal neurons which send inhibitory GABAergic projections to the external segment of the globus pallidus (GPe). These external pallidal neurons then send a GABAergic projection to the STN, which sends an excitatory glutaminergic projection to the output nuclei (SNr & GPi) (Pollack, 2001).

Projections from the cerebral cortex and from the thalamus to the supplementary motor area arise from pyramidal cells and are glutaminergic (excitatory); projections from the striatum, GPe, and GPi arise from medium spiny neurons and are GABAergic (inhibitory; Fitzgerald et al., 2007).

2.2.2 The Limbic Loop

Primarily concerned with the emotional aspects of movement, the limbic loop passes from the inferior prefrontal cortex through the anterior aspect of the striatum
(the nucleus accumbens) and the ventral pallidum before returning to the inferior prefrontal cortex via the mediodorsal nucleus of the thalamus (Fitzgerald et al., 2007). Believed to be responsible for emotional movements such as smiling and gesturing, this route is rich in dopaminergic nerve endings; the reduction in DA levels in People with PD may explain symptoms such as mask-like facial features and a lack of spontaneous gesturing (Fitzgerald et al., 2007). In addition to this, the increased presence of Lewy bodies and Lewy neurites (discussed later in this chapter) in the thalamic components of the limbic loop nuclei may contribute to a wide range of cognitive, emotional, autonomic, somatomotor, and oculomotor dysfunctions seen in PD (Rüb et al., 2002).

2.2.3 The Prefrontal (Cognitive) Loop

Primarily concerned with motor learning and intentions, the cortical connections of the caudate suggest that the prefrontal loop participates in planning complex motor movements (Fitzgerald et al., 2007), executive functioning, working memory, and spatial memory (Kopell & Greenburg, 2008). People with PD that have lesions in the dorsolateral prefrontal cortex exhibit difficulties with flexible thinking, hypothesis generation, maintaining and shifting of cognitive sets, and memory recall (Katzen, 2000). It is also believed that this prefrontal loop is involved in additional aspects of cognitive dysfunction such as reduced verbal fluency, poor organisational skills, reduced insight into symptom presence and severity, the ability to suppress negative emotions, and the experience of pain (Kopell & Greenburg, 2008).

Van Koningsbruggen, Pender, Machado, and Rafal (2009), investigated the role of the basal ganglia in integrating voluntary and reflexive behaviour and found that participants with PD showed impairments in exerting control over oculomotor
reflexes. As saccadic eye movements are easily measured and well understood (Chan, Armstrong, Pari, Riopelle, & Munoz, 2005), they provide a useful method for investigating and quantifying response suppression deficits in PD. Amador, Hood, Schiess, Izor, and Sereno (2006), found that, when compared to control participants, people with PD were slower to initiate saccades on all experimental tasks and had more difficulty inhibiting automatic responses. This finding has been consistent across a number of studies involving a variety of motor, cognitive and oculomotor tasks (van Koningsbruggen et al., 2009), thus indicating a general deficit in response suppression in people with PD (Chan et al., 2005).

2.2.4 The Oculomotor Loop

The oculomotor loop commences in the frontal eye field and posterior parietal cortex, passing through the caudate nucleus and the SNpr (Kimmig, Haubmann, Mergner, & Lucking, 2002). It returns via the ventral anterior nucleus of the thalamus. In addition to this, the SNpr sends an inhibitory GABAergic projection to the superior colliculus where it synapses onto cells controlling automatic saccades. The oculomotor loop is activated when a deliberate saccade is about to be made toward an object. The SNpr acts as a gate for the preparation of saccades by disinhibiting the superior colliculus (Kimmig et al., 2002). For people with PD, neuronal degradation within the SNpr leads to faulty disinhibition of the superior colliculus. As a consequence, saccade initiation tends to be slowed (oculomotor akinesia) and often inadequate, falling short of the intended target (oculomotor hypokinesia) and necessitating additional corrective saccades be made (DeJong & Jones, 1971). Oculomotor bradykinesia, or increased time lapse between visual targets, is the end result (DeJong & Jones, 1971).
2.2.5 Summary

This set of basal ganglia-thalamocortical circuits appears to have a unified role in modulating the operations of the entire frontal lobe (Alexander & Crutcher, 1990). With shared mechanisms and operating in parallel, these circuits influence processes that range from the maintenance and switching of various behavioural sets, via the prefrontal and limbic circuits, and the planning and execution of limb and eye movements, via the motor and oculomotor circuits. While it has been quite well established that these loops originate in different areas of the cortex and project to the basal ganglia, thalamus and frontal cortex in a segregated, organised, and topographic manner, the mixed presentation of symptoms in PD would suggest that there is at least some communication between the circuits (Katzen, 2000).

2.3 Lateralisation of Function and Hemispheric Asymmetries

It is a generally accepted biological phenomenon that some relative functional differences exist between the left and the right sides of the brain, with functional hemispheric specialties being observed for several cognitive functions (Ocklenburg & Gunturkun, 2012). The majority of individuals exhibit right hemisphere dominance for visuo-spatial tasks while the left hemisphere is language and verbal functioning dominant (Fitzgerald et al., 2007; Ocklenburg & Gunturkun, 2012). While initially believed to be a uniquely human characteristic, hemispheric lateralisation has since been proved to be a fundamental principle of nervous system organisation across species and is highly relevant to animal behaviours and survival mechanisms (Ocklenburg & Gunturkun, 2012).
In addition to functional asymmetries between the two hemispheres, structural asymmetries, or anatomical differences such as volume and size, can also be found across a wide range of brain regions (Amunts, 2010).

2.3.1 Subcortical Asymmetries

While hemispheric asymmetries have been widely investigated at a cortical level, less is known about the possibility of subcortical asymmetries and lateralisation of function. There is some research to suggest structural asymmetries exist in the globus pallidus and striatum (Naftali, Torres, & Acker, 1995). However, research has generally been inconsistent or inconclusive, and although structural asymmetries in areas including the subcortical nuclei appear to be non-random in nature, it is more difficult to conclude an overall, organising laterality associated with general functions or behaviours (Whitaker & Ojemann, 1977).

2.3.2 Subcortical Asymmetries and Parkinson’s Disease

Due to the subcortical nature of PD, people who have been diagnosed provide a relatively unique population from which to further investigate the possibility of lateralisation of subcortical functioning. The side of their motor symptom onset can be used to indicate the location of any subcortical degeneration which can, in turn, be used as an independent variable when conducting cognitive testing (Erro et al., 2013).

2.3.2.1 Symptom Asymmetry

As previously mentioned, in as many as 85% of people with PD, motor symptoms will predominately manifest unilaterally, or with at least some degree of
asymmetry (Erro et al., 2013; Yust-Katz, Tesler, Treves, Melamed, & Djaldetti, 2008). In fact, asymmetrical symptom presentation at onset is used as a clinical indicator for differential diagnosis and to separate idiopathic PD from other parkinsonian-like presentations (Erro et al., 2013). While some people with PD who experience initial unilateral symptom onset will go on to develop bilateral symptoms, there is a portion of people with PD who will remain unilaterally affected over the course of the disease (Djaldetti, Ziv, & Melamed, 2006).

Several studies have suggested that lateralised symptom presentation, particularly at onset, is caused by asymmetric degradation of the relevant contralateral brain regions (Kempster, Gibb, Stern, & Lees, 1989; Leenders et al., 1990). It has also been suggested the organisation of the corticostriatal loop indicates that any lateralisation of function displayed at a cortical level may well be replicated at a subcortical level (Cheesman et al., 2005). While this research focused on executive functioning deficits only, through the use of PET scans they were able to show that cognitive functioning in this domain correlated positively with striatal dopamine storage capacity, thus supporting the view that dopaminergic loss in the nigrostriatal pathway contributes to the early cognitive changes seen in people with PD (Cheesman et al., 2005).

2.3.2.2 Side and Type of Motor Symptom Onset and Cognitive Decline

Predominant motor symptom type at disease onset has been differentially linked to the severity of subsequent cognitive decline in PD (Katzen, Levin, & Weiner, 2006). Bradykinesia and rigidity are more commonly associated with cognitive decline, while tremor is not, suggesting that the pathophysiological
degradation responsible for bradykinesia and rigidity may also underlie PD-related cognitive deficits (Katzen et al., 2006).

It is important to note that research into the existence of a link between side and type of motor symptom onset and subsequent cognitive decline in PD have been equivocal to date (Erro et al., 2013; Katzen et al., 2006). Some research has shown clear patterns of lateralisation, whereby people with PD display patterns of cognitive impairment that are characteristic of hemispheric decline that is contralateral to the side of their motor symptom onset (Huber, Miller, Bohaska, & Christy, 1992; Spicer, Roberts, & LeWitt, 1988; Verreyt et al., 2012). However, other studies have shown no relationship whatsoever (Erro et al., 2013), or relationships that follow very different patterns, for example, left sided motor onset equals widespread cognitive deficit, while right sided motor onset equals minimal, if any, cognitive deficit (Direnfeld et al., 1984). In addition to this, the majority of early research in the area used side and type of motor symptom at time of assessment, as opposed to at time of disease diagnosis. It has been suggested that the type of symptom at disease onset may be more critically related to the underlying neuropathological dysfunction, which may in turn influence disease course and extent of cognitive dysfunction (Katzen, 2000). These methodological differences and subsequent variability in conclusions highlight the need for additional research in the area.

Current side and type of motor symptom

Cooper et al. (2009) investigated whether right sided motor symptoms could account for cognitive deficits in specific cognitive domains, or more specifically, whether right sided motor symptoms related to performance in the domains of verbal memory, verbal fluency, executive functioning, and visuospatial skills. Their
participants \( n = 117 \) were assessed for motor symptom presentation using form three of the Unified Parkinson’s Disease Rating Scale (UPDRS), and cognitive functioning using a battery of neuropsychological tests. Results indicated a significant association between right sided motor impairment and verbal memory, visuoperceptual skills, and verbal fluency. They found no significant associations for left sided motor impairment and any cognitive domain, and no association between executive functioning and left or right sided motor symptom presentation.

Additional analysis examining the mediating effects of general cognitive functioning as measured by the Disability Rating Scale (DRS) and the Mini Mental State Examination (MMSE; Folstein, Folstein, & McHugh, 1975) on these results showed that significance was maintained for right sided motor symptom presentation and both verbal memory and visuoperceptual performance.

**Side and type of motor symptom at disease onset**

Viitanin, Mortimer, and Webster (1994) used retrospective data to investigate associations between side of motor symptom presentation at the point of disease onset and subsequent cognitive decline. Significant results were found when examining bilateral versus unilateral motor symptom onset, with bilateral onset predictive of a more severe cognitive decline profile as measured by the MMSE. However, further examinations into side (left/right), type (tremor/rigidity/bradykinesia), and location (upper/lower extremity) of initial symptom presentation were not consistently related to future cognitive impairment as measured by the MMSE, although it is important to note that the MMSE is a very brief screen for cognitive impairment.
Dewey et al. (2012) used a cohort of 114 people diagnosed with idiopathic PD to investigate whether side and type of motor symptom presentation at point of disease onset could predict risk of future cognitive impairment. They also investigated the role of motor symptom onset in predicting future risk of depression. The participants were split into four groups on the basis of side (left or right) and type (tremor or bradykinesia/rigidity) of initial motor symptom presentation and administered tests to assess current cognitive functioning and depression levels. People with bilateral onset were excluded.

Results indicated side and type of motor symptoms at disease onset were not associated with impairment in any of the cognitive domains assessed. Their battery of neuropsychological assessments included a brief screen for overall cognition and several additional measures that more closely examined specific cognitive functions such as processing speed, attention, verbal and non-verbal memory, executive functioning, working memory, and language. Dewey et al. (2012) concluded that their findings fit with a model of PD that posits the cortical pathways integral to cognitive functioning become involved by Lewy pathology only relatively late in the disease process.

Katzen et al. (2006) also investigated the role of side and type of motor symptom presentation at disease onset in the later development of cognitive decline. Idiopathic PD diagnosed participants \((n = 69)\) were divided into four groups on the basis of side and type of initial motor symptom presentation, those with bilateral motor symptom onset were excluded from the study. In addition to this, a cohort of healthy controls \((n = 40)\) were also examined. Results indicated people with PD with right sided tremor onset performed significantly better on a battery of neuropsychological tests than all three of the other PD groups and comparatively
with the healthy control group. In contrast, the three remaining PD groups showed wide-spread cognitive decline. These findings were in keeping with previous studies that had found right sided tremor onset to be predictive of a more benign disease progression profile. Katzen et al. (2006) also concluded that it is likely an intricate relationship exists between motor symptoms and side of disease onset and that it is a combination of these factors that influence the course and extent of subsequent cognitive decline.

*De novo Parkinson’s disease*

In an attempt to diminish the impact of dopaminergic medications on experimental results, Poletti et al. (2013), examined 108 newly diagnosed and drug naïve people with PD with a unilateral motor symptom presentation or a clear motor symptom asymmetry. They found that that there were no significant differences between the groups (right or left) on measures of cognitive functioning. Additional analyses were conducted to examine any potential relationships between severity of motor symptom laterality and cognitive performance. A significant correlation was found between right side symptom severity and set-shifting as measured by the Trail Making Test. Significant correlations were also found between left side symptom severity and phonemic fluency, as well as with tests with a visuospatial component (Rey-Osterrieth Complex Figure – copy & immediate recall, & Raven’s Progressive Matrices).

In conclusion, Poletti et al. (2013) found that motor symptom lateralisation is not associated with specific cognitive characteristics in the early, untreated stages of the disease, therefore suggesting that any potential differences are more likely to be found as the disease progresses.
In support of this finding, Erro et al. (2013) also found that side of motor symptom onset did not affect cognitive performance in newly diagnosed, drug-naïve people with PD. Their results indicated that while 36.2% of their participants \( n = 69 \) showed some signs of cognitive decline, these participants were spread across all testing groups and there were no significant differences between groups irrespective of side or type of motor symptom presentation on tests of neuropsychological functioning.

Arnaldi et al. (2012) also used newly diagnosed, drug naïve people with PD, and examined which clinical, neuropsychological and/or functional neuroimaging characteristics at disease onset were predictive of cognitive decline approximately four years later. They found that UPDRS scores and caudate DA transporter uptake in the less affected hemisphere were predictive of executive and visuospatial decline, while verbal memory and language decline were predicted by caudate DA transporter uptake and brain perfusion in a posterior parieto-temporal area of the less affected hemisphere. They found no significant effects for age, cognitive functioning at baseline, or levodopa equivalent dose at the time of follow-up. These results indicate an important role for neuroimaging at disease onset.

2.3.2.3 Summary

These disparate findings are in keeping with the vast majority of research conducted on the possibility of a subcortical motor-non motor symptom link, where results have been contradictory and/or inconclusive. Possible explanations for these discrepancies include the methodological differences between the studies, with variables such as time since onset, treatment length and treatment type (none, medication, surgery, combination treatments) difficult to control for and producing
results that are difficult to generalise across the wider PD population. For example, Erro et al. (2013) conducted their research on newly diagnosed people who had yet to be treated, and while this makes it possible to eliminate the effects of medication on research results, it may be problematic to extrapolate their findings to people with PD in general. The majority of researchers conclude that additional investigation in this area is required (Erro et al., 2013; Huber et al., 1992; Katzen et al., 2006; Lowitt, Howell, & Brendel, 2005).

Bradykinesia and akinesia are cardinal motor symptoms that have consistently been linked to poorer cognitive outcomes for people with PD (Katzen, 2000). As previously mentioned, bradykinesia is the result of reduced DA levels in the caudate nucleus and a failure of the output nuclei of the basal ganglia (the GPi & the SNpr) to reinforce the cortical mechanisms that prepare and execute movement commands (Agostino, et al., 2003). While there have been some studies that have failed to find relationships between bradykinesia/akinesia and cognitive decline (Jankovic et al., 1990; Richards et al., 1993), others have found positive correlations between severity of bradykinesia/akinesia and cognitive decline (Katzen, 2000). These findings highlight the importance of including tasks that detect motor slowing through, for example, manual dexterity and motor speed, in future research.

The pathophysiology of rigidity is less clear cut, with some researchers suggesting that the increase in muscle tone may be caused by long-loop reflexes originating in muscle spindles and running through cortical relays, while others dispute this, suggesting that the theory cannot account for all patterns of rigidity present in PD (Santens, Boon, Van Roost, & Caemaert, 2003). As with rigidity, the exact pathophysiology of tremor in PD has been widely questioned, with specific
regions of the thalamus, as well as the STN, targets for surgical treatment (Rodriguez et al., 1998), however exact consensus has yet to be reached (Santen, 2003).

2.4 The Role of Dopamine in the Basal Ganglia

Dopamine (DA) is a monoamine neurotransmitter from the catecholamine (CA) family and plays an integral role in the control of fine motor movements, and in higher cortical functions such as attention, working memory, learning, sleep regulation, decision making and response to rewards (Beaulieu & Gainetdinov, 2011; Tritsch & Sabatini, 2012). DA also plays a significant physiological role in the periphery, regulating olfactory, hormonal and sympathetic responses, as well as retinal processes, cardiovascular and renal functioning, and the immune system (Beaulieu & Gainetdinov, 2011).

DA derives its name from its chemical structure; an amine group (NH$_2$) linked to a catechol structure, dihydroxyphenethylamine and is synthesised in the cells by one of three amino acids (Beaulieu & Gainetdinov, 2011). These amino acids are L-Tyrosine, L-Phenylalanine, and L-DOPA, with L-Tyrosine being the most common of the three (Fitzgerald et al., 2007).

Dopaminergic innervations are the most prominent in the brain, with four major DA pathways identified; the nigrostriatal, mesolimbic, mesocortical and tuberoinfundibular systems (Beaulieu & Gainetdinov, 2011). There are five DA receptors that can be divided into two groups, D1-class (containing receptors D1 and D5) and D2-class (containing receptors D2, D3 & D4), on the basis of their genetic, structural, pharmacological and biochemical properties (Beaulieu & Gainetdinov, 2011; Tritsch & Sabatini, 2012). In the striatum, for example, the two output pathways (direct & indirect) are affected differently by the dopaminergic projections.
from the SNpc. Neurons in the direct pathway contain D1 receptors that facilitate transmission, while neurons in the indirect pathway contain D2 receptors that reduce transmission (DeLong, 2000). Despite the fact that their synaptic actions are different, the D1 and D2 inputs lead to the same net effect, reducing inhibition of the thalamocortical neurons and facilitating cortex-initiated movements.

Synaptic vesicles transport and store a number of neurotransmitters, including DA (Alter, Lenzi, Bernstein, & Miller, 2013). Upon synthesis, DA is transported to and then stored in synaptic vesicles until calcium influx and an action potential occurs, at which point the vesicles merge with the presynaptic cell membrane via exocytosis, causing a release of DA in the synapse (Alter et al., 2013). Once in the synapse DA will bind to both postsynaptic and presynaptic DA receptors. DA that binds to the presynaptic DA receptors can have either an excitatory or an inhibitory effect depending the receptor’s electrical potential. Those with an inhibitory potential play a crucial role in maintaining DA levels in certain pathways by inhibiting neurotransmitter synthesis and release following acute disruption (Beaulieu & Gainetinov, 2011).

Post synaptic release, DA is removed from the synaptic cleft via reuptake and is then either recycled by dopaminergic neurons or degraded by glial cells (Meiser et al., 2013). Recycled DA is returned to the presynaptic cells via either the dopamine transporter or the plasma membrane monoamine transporter. Once returned it is repackaged into the synaptic vesicles. DA is eventually broken down into inactive metabolites by monoamine oxidase (MAO) and catechol-O-methyltransferase (COMT). It maybe then undergo and additional phase two conjugation reaction before being excreted in the urine (Meiser et al., 2013). While DA is also found in some food items, unlike the amino acids it is synthesised from (L-Tyrosine, L-
Phenylalanine, & L-DOPA), DA itself is incapable of crossing the blood-brain barrier. DA must be formed within the blood-brain barrier in order to carry out its functions (Harvey & Champe, 2008).

Basal ganglia structures, including the striatum, the GPe and GPi, parts of the ventral pallidum and the STN, are known to be innervated by DA neurons that project from the midbrain (Bjorklund & Dunnett, 2007; Robertson, 1992; Tritsch & Sabatini, 2012). These midbrain DA neurons can directly modulate the activity of the basal ganglia output neurons at palladial, subthalamic and nigral levels. Within the SN, DA is released from dendritic terminals derived from DA neurons in the ventral tier of the SNpc, with extensions throughout large parts of the SNpr (Bjorklund & Dunnett, 2007), with a dopaminergic nigrostriatal pathway projecting from the substantia nigra to the striatum. This pathway controls a motor loop of neurons that feed forward to the motor cortex. These ventral tier DA neurons appear crucially placed to regulate certain aspects of neurotransmission in the circuitry of the basal ganglia. Dendritic DA release provides a mechanism by which nigral DA neurons regulate the activity of not only the DA neurons themselves, but also the release of GABA within the SNr and the activity of its efferent projections (Robertson, 1992).

2.4.1 Dopamine and the Development of Parkinson’s Disease

Dopamine degradation plays a causal role in the development of PD, with symptoms becoming manifest following ongoing nigral dopaminergic presynaptic neuron loss, leading to a reduction of approximately 70-80% in striatal dopamine levels (Müller, 2012). DA depletion in the striatum leads to impaired movement due to an increase in activity in the output nuclei. This has the flow-on effect of increasing inhibition of thalamocortical neurons that would normally facilitate
movement initiation (DeLong, 2000). Dopaminergic synapses are also located in the GPe, GPi, the STN, and both regions of the substantia nigra.

Additionally, Whone, Moore, Piccini, and Brooks (2003) observed a compensatory increase in $^{18}$F-flurodopa uptake in the GPi in early stages of PD progression that is not observed at more advanced stages of the disease, with their participants showing an absence of clinical progression despite continued nigrostriatal projection degradation. It is therefore possible that enhanced DA projection activity in the GPi is capable of maintaining normal motor functioning when the nigrostriatal system starts to fail (Bjorklund & Dunnett, 2007; Whone et al., 2003).

2.4.2 Dopamine and Motor Symptoms

Motor symptoms such as akinesia and rigidity, as well as tremor to a lesser extent, respond positively to dopaminergic stimulation (Müller, 2012). A number of pharmacological treatments have been developed for PD that are designed to primarily influence DA levels, highlighting the importance of DA degradation in initial disease manifestation. Monoamine-oxidase B inhibitors (MAO-B) can be used to stabilise available dopamine levels in the synaptic cleft, causing prolonged dopaminergic activity, while DA agonists act directly on post-synaptic DA receptors. NMDA-antagonists improve motor symptoms, including some motor complications such as dyskinesia, via dopamine stimulation (Müller, 2012). However, these treatments can cause potentially significant side-effects, particularly of the non-motor variety, such as psychiatric disorders, hypostatic hypotension, nausea/vomiting, sleep disturbances, and oedema (Smith, Wichmann, Factor, & DeLong, 2012).
2.4.3 The Role of L-DOPA

While MAO-B inhibitors, DA agonists, and NMDA antagonists can all be used with varying degrees of success (Lyons & Pahwa, 2011; Müller, 2012), orally administered L-DOPA, one of three chemical precursors for dopamine, remains the gold standard for treatment of motor symptoms in PD (Smith et al., 2012). However, L-DOPA is not without its problems as it is rapidly metabolised in the liver and intestinal mucosa by dopa decarboxylase, and in the periphery of the brain by COMT (Waters, 2000). As a result of these two processes it is believed that less than 1% of the L-DOPA actually crosses the blood brain barrier. Peripheral metabolism of L-DOPA can also cause additional side effects such as dyskinesia, nausea and vomiting.

Several pharmacological treatments for PD involve co-administering L-DOPA and one of several COMT and/or dopa decarboxylase inhibitors. This has the effect of reducing the amount of L-DOPA metabolised in the periphery, thus increasing the amount of L-DOPA available for transport to the brain (Waters, 2000) and decreasing the L-DOPA dose required for efficacious treatment (Müller, 2012). Decreased L-DOPA dosage can help to ameliorate side-effects such as nausea and vomiting, while co-administered MAO-B inhibitors, DA agonists and/or NMDA antagonists can assist in dealing with motor complications (Gazewood et al., 2013).

2.4.4 Dopamine and Non-Motor Symptoms

It has been previously suggested that while DA replacement therapies can have a significant impact on motor symptoms in PD, they have a less beneficial, and in some instances causative, effect on non-motor symptoms such as mood, cognition, and impulse control (Ahlskog, 2007; Smith et al., 2012). Ahlskog went on to suggest
that future pharmacological research needed to move away from DA replacement therapies and towards alternative treatments that would serve to adequately address these non-motor symptoms. More recently, Antonini and Albin (2013) have argued against this as an approach, suggesting that the basal ganglia have been implicated in many of the non-motor symptoms experienced by people with PD and that DA still has a vital role to play. Various DA replacement therapies, including both oral and intraduodenal infusions of levodopa, lead to beneficial effects on a wide range of non-motor symptom scales including measures of sleep disorders, depression, cardiovascular and gastrointestinal functioning, attention and memory, and sexual functioning (Barone et al., 2010; Honig et al., 2009; Trenkwalder et al., 2011).

The key to implementing DA replacement treatment regimes in people with PD is to ensure a targeted and individualised approach that considers the specific motor/non-motor symptom presentation of the patient and works to maximise therapeutic efficacy and minimise development of side-effects. Lyons and Pahwa (2011) emphasise the point that PD symptom management requires accurate recognition of all the motor and non-motor symptoms a patient is experiencing, as well as an understanding of the ways motor symptoms treatments, such as DA replacement therapies, can both alleviate and exacerbate specific non-motor symptoms.

While the most recognised DA-related disorder is PD, it has been suggested that the neurotransmitter may also play a significant role in the development of several other conditions, including schizophrenia, addiction, Huntington’s disease, ADHD, Tourette’s syndrome, bipolar disorder and depression, and dyskinesia (Beaulieu & Gainetdinov, 2011).
2.4.5 *Lewy Bodies, Lewy Neurites and α-Synuclein*

Pathologically, PD is characterised by accumulated proteins (Lewy bodies and Lewy neurites) in the perikarya, dendrites, and axons of DA synthesising neurons in the substantia nigra pars compacta (SNc) as well as in other regions of the autonomic nervous system (Cools, 1984; Olanow & Brundin, 2013). Rüb et al. (2002) found that Lewy bodies and Lewy neurites consistently develop only in distinct thalamic nuclei, and with very little inter-patient variability. In addition to this, they were able to conclude that the presence of Lewy bodies and Lewy neurites is not a part of normal ageing as even the very elderly healthy controls in their experiment did not show signs of this pathology.

Both Lewy bodies and Lewy neurites are made up of a granular core surrounded by a filamentous halo primarily comprised of a neurofilament and α-synuclein. α-synuclein is a small, acidic, unfolded protein molecule localised in neuronal and glial cells of the SN, thalamus, neocortex and hippocampus, with the SN and the limbic loop assigned regions of the thalamus being particularly affected (Mullin & Schapira, 2013; Rüb, 2002). In its unaltered form, α-synuclein is hydrophilic and associated with synaptic vesicle and synaptic plasma membranes (Rüb, 2002). Formation of pathological α-synuclein inclusions occurs via a multistep process that begins with the misfolding of normal soluble proteins and their association into higher order oligomers (Volpicelli-Daley et al., 2011). This is followed by the development of amyloid fibrils that form disease specific (PD or Alzheimer’s disease for example) inclusions (in PD; Lewy bodies & Lewy neurites). Volpicelli-Daley et al (2011) showed that an accumulation of pathologic α-synuclein caused selective decreases in synaptic proteins, neuronal excitability and connectivity impairments, and neuronal death.
2.5 Summary

The basal ganglia refers to subcortical areas of the basal forebrain and midbrain known to be involved in the control of movement and other higher cortical functions (Fitzgerald et al., 2007). The basal ganglia consists of five principal nuclei: the caudate and putamen (collectively known as the striatum), the globus pallidus, the substantia nigra, and the STN. Recent evidence has suggested an expanded role for the basal ganglia into areas of both motor and cognitive functioning (Leisman, Melillo, & Carrick, 2013). DA plays a crucial role in the control of fine motor movements as well as in some higher cortical functions such as attention, working memory, and sleep regulation. A number of basal ganglia structures are known to be innervated by DA neurons that project from the midbrain. DA degradation is a causative factor in the development of PD, with cardinal symptoms becoming manifest following critical nigral dopaminergic presynaptic neuron loss. Orally administered L-DOPA, a DA precursor, remains the gold standard pharmacological approach for PD motor symptoms, further highlighting the role of DA degradation in disease manifestation. More recent research has also found positive effects for dopamine replacement therapies on non-motor symptoms such as sleep regulation, depression, attention, and memory.

At present, very little is known about the possibility of subcortical lateralisation of function. As PD is a subcortical disorder, people with PD provide a unique population from which to examine this. Current research has been equivocal, with some results indicating a link between side of onset (right or left) and cognitive decline patterns and severity, while others have found no links. It is important to
note that this particular area of research is in its infancy and additional research is required before definitive conclusions can be made.
CHAPTER THREE

Neuropsychological Assessment of Motor and Non Motor Symptoms

3.1 Motor Symptom Assessment

Typically, the initial presentation of motor symptoms in PD has an asymmetric quality, with most people experiencing disturbances unilaterally (Banich, 1997; Fitzgerald et al., 2007; Uitti, Baba, Wszolek, & Putzke, 2005;). This presentation can persist for years and, even in the later stages of disease progression, it is common for one side of the body to be more severely incapacitated than the other (Holtgraves, McNamara, Cappaert, & Durso, 2009).

As previously mentioned, cardinal motor symptoms typically associated with Parkinson’s disease include muscle rigidity, tremors, bradykinesia, a loss of postural reflexes and akinesia (Gazewood et al., 2013; Verreyt et al., 2011).

As with most aspects of PD, the motor symptoms that manifest can be very difficult to gauge for severity or degree of impairment, with a pure motor symptom severity rating difficult to obtain.

3.1.1 Brain Injury and Rehabilitation Trust Memory and Information Processing Battery

The Brain Injury and Rehabilitation Trust Memory and Information Processing Battery (BMIPB; Coughlan, Oddy, & Crawford, 2007), is an assessment battery made up of six subtests that assess a range of skills including immediate and delayed recall, visual memory, information processing speed, and motor speed.
3.1.1.1 Information Processing and Motor Speed

With regard to the assessment of motor speed, the information processing speed subtest comprises two similar cancellation tasks. In the first, the subject is required to scan a number of lines made up of five numbers and to cross out the second highest, whereas in the second the subject simply crosses out the only number on each line. From the results of these two tasks, it is possible to calculate both a pure information processing speed score for the subject as well as a motor speed score (Coughlan et al., 2007). The BMIPB is seen as a potentially useful tool for tracking cognitive decline in people with neurodegenerative disorders (Morris & Brooks, 2013).

3.1.2 Finger Oscillation (Tapping) Test

The Finger Oscillation (Tapping) Test is the most widely used test of manual dexterity. It is a subtest of the Halstead-Reiten Neuropsychological Test Battery (Reitan & Wolfson, 1993), and consists of a tapping key attached to a counter that calculates the number of complete taps achieved in each ten second trial (Lezak et al., 2004).

This test was originally developed to assess motor control and speed, and has also been used to detect neurological damage via motor dysfunction (Eng et al., 2013). As finger tapping requires speed, coordination and pacing it can be significantly affected by slowed responses, poor or disrupted attention, and the individual’s level of alertness.

Standard administration instructions for the Finger Oscillation Test require five consecutive trials within a five-point range for each hand be achieved, starting with the dominant hand (Reitan & Wolfson, 1993). The overall score is comprised of
the average of each of the five trials. All standardisation data for the Finger Oscillation Test is based on consecutive administration trials and in recent research, Eng and colleagues (2013) showed that switching to an alternating administration method significantly influences the results for both dominant and non-dominant trials. They concluded that although the alternating method produced more consistent scores, with a smaller standard deviation than the original norms, until new norms could be established, maintaining the consecutive trials administration method was integral for accurate interpretation.

Motor performance with the dominant hand is typically superior to the motor performance of the non-dominant hand and, in addition to this; performance is typically inferior for the hand that is contralateral to the side of any preceding brain injury or area of neurological degeneration (Spreen & Strauss, 1998). As people with PD typically present with unilateral motor symptom onset, finger tapping test results often show considerable variability when comparing left with right (Jobbagy, Harcos, Karoly, & Fazekas, 2005).

Research pertaining to individuals with more severe motor impairments, such as those seen in PD, suggests the necessity for five successful trials that all fall within a five point range means some additional trials may be required (Jarvis & Barth, 1994).

Additional research (Yang et al., 2003) showed a relationship between performance on the Finger Tapping Test and striatal dopamine D2 receptor density, with poorer performance indicative of lower levels of receptor density.
3.1.3 *Hand Dynamometer*

The hand dynamometer is a device used to assess grip and muscle strength, as well as muscle function (Roberts et al., 2011). Dodrill (1978) evaluated the sensitivity of the hand dynamometer for detecting the presence and lateralisation of brain damage. He compared this assessment device to the Tapping Test (Finger Oscillation Test) and to the Tactual Performance Test and found that while all three methods significantly discriminated between brain injured participants and neurotypical controls; the hand dynamometer was most accurate for detecting injury lateralisation. In addition to this, the hand dynamometer is considered a more cognitively simple test to the Finger Tapping Test as it requires less skill and adaptation to perform, particularly with regard to pacing, motor speed and coordination, and when switching to carry out the task with the non-preferred hand (Strauss, Sherman, & Spreen, 2006).

Typically, grip strength will begin to decline after mid-life, with accelerated loss occurring due to increase in age. Grip strength has been shown to have predictive validity, with low values associated with falls, disability, and impaired health-related quality of life. Low values have also been shown to be predictive of prolonged length of hospital stays and increased mortality (Bohannon, 2008; Roberts et al., 2011).

In addition to its predictive qualities, the hand dynamometer presents as a useful assessment tool due to its portability, low cost, and ease of administration (Bohannon, 2008).
3.2 Non-Motor Symptom Assessment

3.2.1 Cognitive Assessment

As previously mentioned, people diagnosed with PD face the possibility of developing a myriad cognitive changes ranging from mild impairment to PD dementia (Emre, 2004; Poewe et al., 2008). Despite agreement as to the existence of cognitive dysfunction in PD, controversy still exists regarding the nature and extent of these symptoms.

Adding to difficulties establishing a clear understanding of cognitive decline in PD, the assessment process itself can be complicated and time consuming. Motor symptoms, fatigue, pain, the effects of medications, anxiety, and depression can all interfere with the assessment process, with timed tests and tests involving a motor component, such as drawing or writing, particularly susceptible (Miereles & Massano, 2012).

Typically, cognitive changes in PD manifest as impairments in attention, executive and visuo-spatial functions, with memory encoding and language abnormalities playing a less significant role than they do in Alzheimer’s disease (Poewe et al., 2008). Symptoms of prefrontal dysfunction, such as difficulties initiating responses, difficulties with serial and temporal ordering and executive planning impairments are also a common feature of PD (Freedman, 1990).

In the recently developed diagnostic criteria for MCI in PD, it is suggested that cognitive assessment batteries include tests designed to cover the following five domains: executive functioning, attention and working memory, language, memory, and visuospatial functioning (Litvan et al., 2012).

Loranger, Goodall, McDowell, Lee and Sweet (1972), found that people with PD exhibited more deficits in tasks relating to performance IQ than they did in tasks
relating to verbal IQ. The notion of differentiating between performance and verbal IQ is grounded in the Wechsler intelligence tests whereby each refer to a score derived by the administration of selected subtests. Performance IQ includes tests such as block design, symbol search, and matrix reasoning, while verbal IQ includes vocabulary, information, and digit span. It has been suggested that the more crystallised, over-learned nature of tasks such as vocabulary and information make them less susceptible to disruption, whereas performance based tasks like digit symbol coding are more reliant upon visuospatial processing and speeded motor responding; cognitive abilities known to be affected by PD (Katzen, 2000).

The assessment of language skills in people with PD can be complicated by the presence of motor symptoms that affect articulation and motor speed. When assessing language skills it is important to differentiate them from any speech problems caused solely by motor deficits (Levin, Tomer, & Rey, 1992).

Executive functioning is a term used to refer to capabilities that include being able to create a plan and follow through with it, to adapt flexibly, to sequence and to prioritise, to make cognitive estimations, and to interact in a socially astute manner (Banich, 1997). Impairments in executive functioning can lead to deficits in initiation, cessation and control of actions, perseveration, or the tendency to engage in repetitive behaviours, impairments in abstract reasoning, and a lack of cognitive flexibility. People with PD typically exhibit executive functioning deficits (Banich, 1997; Weintraub et al., 2005), with impairment linked to degeneration in the frontal-subcortical tracts (Weintraub et al., 2005).

Visuospatial deficits are the most widely observed cognitive symptoms in PD with Levin et al. (1992) defining visuospatial ability as a group of complex
behaviours including facial recognition, visual analysis and synthesis, spatial attention, and judgement of direction, orientation and distance.

To date, studies examining the effects of PD on memory have been unable to determine whether people are more likely to experience specific memory impairments, or a more global decline in overall memory performance (Katzen, 2000). In addition to this, further studies have shown it can be difficult to differentiate between pure memory deficits and memory difficulties that are compounded by executive functioning deficits, such as susceptibility to interference, and poor implementation of organisational tools.

It is possible to assess these deficits using a range of established neuropsychological measures in much the same way cognitive deficits are assessed in other clinical populations. The main confounding factor present in PD, and not so much of an issue in other disorders, is the presence of motor deficits which can significantly impact on the patient’s physical ability to complete a task. When selecting assessment methods for a PD population it is important to take this into consideration.

3.2.1.1 Repeatable Battery for the Assessment of Neuropsychological Status

The Repeatable Battery for the Assessment of Neuropsychological Status (RBANS; Randolph, 1998) was initially designed as a brief screening tool for assessing adults with suspected dementia and is comprised of eight sub-tests, three of which comprise two or more components, bringing to total tasks to complete to twelve. The battery can also be used as a general screening tool to assess the neuropsychological status of adults with neurological injury or disease (Randolph, 1998). The RBANS is described as repeatable as it is made up of two equivalent
forms to allow for assessing change over time, and can typically be administered within half an hour (Lezak et al., 2004).

The ten subtests are used to comprise five index scores and a summary measure with each index score reported as a standard score with a mean of 100 and a standard deviation of 15. In addition to an overall score, this assessment also yields index scores for immediate memory, language, attention and delayed memory, and visuo-spatial/constructional tasks (Lezak et al., 2004).

The subtests, most of which have been derived from other previously empirically validated neuropsychological measures, are:

- **List Learning and Story Memory** (Immediate Memory Index)
- **Figure Copy and Line Orientation** (Visuospatial/Constructional Index)
- **Picture Naming and Semantic Fluency** (Language Index)
- **Digit Span and Coding** (Attention Index)
- **List Recall, List Recognition, Story Recall and Figure Recall** (Delayed Memory Index)

The word lists and the story recall tasks are used to assess immediate and delayed verbal recall, while assessment of language is completed using both confrontation naming and semantic fluency tasks.

Complex visuo-spatial processing and visual memory are assessed using a complex figure task reminiscent of the original Complex Figure Task (Rey, 1941) and the Rey Osterrieth Complex Figure (Osterrieth, 1944) as well as a modification of Benton’s Judgement of Line Orientation task (Benton, Varney, & Hamsher, 1978). The digit span and coding tasks are similar to those found in Weschler’s test batteries.
and are used to assess attention levels.

The RBANS can be administered to individuals aged twenty to eighty nine years of age with normative data available for six age groups that span this time frame (20-39, 40-49, 50-59, 60-69, 70-79, 80-89). The authors suggest that caution is taken when interpreting index scores, particularly when the assessed individual is young or not yet showing signs of overt cognitive decline (Randolph, 1998). On several sub-tests even just one or two incorrect answers can have the associated index score plummeting and it is suggested that individual sub-test characteristics be investigated for additional interpretive information when this occurs, particularly if a subtest scores appears unusually low when compared to the other subtests.

In addition to developing normative data for use with a wide range of cognitively impaired individuals, Randolph (1998) also provided information regarding how the RBANS can be used to differentiate people with cortical dementias such as Alzheimer’s disease from those with sub-cortical degenerative disorders such as Huntington’s disease, ischemic cardiovascular disease and Parkinson’s disease using a ‘cortical-sub-cortical deviation score’. Additional research into this claim appears to support Randolph’s findings (Beatty et al., 2003; Fink, McCrae, & Randolph, 1998). People with cortical dementias tend to perform more poorly on tests of language and delayed memory, whereas those with suspected sub-cortical degeneration perform more poorly on tests of attention, visuospatial processing and visual memory (Beatty et al., 2003; Cummings, 1990). As the RBANS consists of a number of subtests that mirror those suggested by Litvan et al. (2012) for assessing mild cognitive decline (subtests such as line orientation, story memory, and list learning for example), it presents as a useful tool for a PD population.
While not available in the original version of the RBANS manual, upon request it is possible for clinicians to obtain normative data for the individual subtests allowing for a more detailed interpretation of results where required (Lezak et al., 2004).

This particular battery has been found to be a more useful tool for assessing those with mild dementia, particularly when compared to its three main rivals, the Mini Mental State Exam (MMSE; Folstein, Folstein, & McHugh, 1975), and the Dementia Rating Scale, (DRS-2; Mattis, 1988), both of which are basic screening measures, and the Wechsler Memory Scale IV (WMS-IV; Wechsler, 2009). As the RBANS was initially designed for an older adult population, the degree of difficulty of the tasks is more appropriate than those of the WMS, where tasks have been established to avoid ceiling effects in younger people, leaving performance at the lower end of the scale more difficult to interpret (Lezak et al., 2004).

Suggested weaknesses of the RBANS include a lack of subtests investigating executive functioning, motor speed, information processing and category fluency, however as the administration time of the RBANS is relatively brief, it is possible to supplement this battery with additional assessments that target these areas.

3.2.1.2 Controlled Oral Word Association Test

The Controlled Oral Word Association Test consists of three word production trials conducted over one minute each. During initial test development, the letters used were F, A and S. Additionally, developed as part of Benton and Hamsher’s (1989) Multilingual Aphasia Examination, other letter combinations have also been used in research, including C-F-L, and P-R-W.

In each three letter set, the letters have been selected according to the
frequency of use of English language words starting with that letter. In all sets, the first letter has a relatively high frequency; the second letter has a somewhat lower frequency, while the third letter is even lower again (Lezak et al., 2004). Participants are instructed to verbalise as many words as they can spontaneously come up with over a one minute time period. They are told that proper nouns, numbers and the same word presented with a different suffix are not acceptable.

This test is scored by adding all correct words from the three trials together to obtain an overall score which is then adjusted for age, sex and education. It is then possible to convert this adjusted score to a percentile.

3.2.1.3 Brixton Spatial Anticipation Test

The Brixton Spatial Anticipation Test comprises one half of the Hayling and Brixton Tests and is an assessment of concept formation, measuring the ability to detect rules in sequences of stimuli. These rules vary without warning and each current rule cannot be triggered by any perceptually salient information present in the stimuli itself (Strauss et al., 2006). The Brixton Spatial Anticipation Test is a perceptually simple task that requires only verbal responses, thus making it appropriate for a motor function impaired population (Burgess & Shallice, 1997).

Presented in a booklet, the subject is shown a stimulus page where they are informed that the coloured circle moves around according to various patterns that change without warning (Lezak et al., 2004). Participants are then asked to predict the movement of the coloured circle among ten possible orientations. The dot moves about the page according to a rule that is not known by the subject. Additionally, this rule changes unpredictably and without warning, meaning that once a rule has been identified the subject cannot anticipate the next change. The subject is simply
required to point at the page or verbalise their guess, making it a suitable assessment for individuals with speech or motor deficits.

Administration time is approximately five minutes and the test is suitable for use in those aged 18 – 80. Normative data was developed using 121 control participants and 77 participants from a clinical population and the results yield three different measures of executive functioning which can be considered separately or combined into a total score.

Errors made by the participants are recorded as either perseverative errors, an application of another incorrect rule, or as a bizarre response or guesses (Groom et al., 1999).

Initially, age based normative data was limited however Bielak, Mansueti, Strauss, and Dixon (2006) carried out an investigation aimed at developing normative data for older adults, while van den Berg et al. (2009) investigated age and education adjusted regression based norms for a variety of populations, including a control group of healthy older individuals (mean age 67), participants with mild cognitive impairment and early dementia, stroke, psychiatric disorders, diabetes mellitus and Korsakoff’s syndrome. From this research they were able to establish additional norms for older individuals as well as verify the validity of the measure across those clinical groups mentioned (Bielak et al., 2006; van den Berg et al., 2009).

Although this assessment is similar to the Wisconsin Card Sorting Test where the participant also has to identify arbitrary rules which change without warning, there are several key differences between the two. For example, when scoring the Brixton Spatial Anticipation Test it is possible to estimate the amount of guessing that took place during administration (Groom et al., 1999). Currently, no research
exists on the specific use of the Brixton Spatial Anticipation Test in a Parkinson’s disease population (Kessels, Mimpen, Melis, & Olde Rikkert, 2009).

3.2.1.4 Trail Making Test (Parts A and B)

The Trail Making Test is an easily administered two part test of scanning and visuo-motor tracking, divided attention and cognitive flexibility (Lezak et al., 2004). Part A consists of the participants drawing lines to connect consecutive numbers on a work sheet and while conceptually very similar, part B has been designed as a more complex task (switching between numbers & letters) where cognitive flexibility is crucial.

Originally standardised by Partington and Leiter (1949), the normative data varied significantly depending on the clinical group in question and the era in which they were assessed, with completion times increasing for each decade (Lezak et al., 2004). Age, education, and sex (to a lesser degree) all play a significant role in the individual’s overall result, particularly on part B of the assessment. Despite the variability in early normative data, more recently developed cut off scores devised using age and education adjusted norms have proven themselves reliable. Sanchez-Cubillo et al. (2009) investigated the construct validity of the Trail Making Test with the aim of clarifying which cognitive mechanisms underlie performance on this test. Their results suggested that scores on part A are a reflection of visuoperceptual abilities, while part B primarily reflects working memory, sequencing, and task-switching abilities. A comparison of part A and part B scores appeared to minimise the visuoperceptual and working memory demands of the test, leaving a relatively pure indication of executive control abilities (Sanchez-Cubillo et al., 2009).

Higginson, Lanni, Sigvardt, and Disbrow (2013), used part B of the Trail
Making Test to predict ability to carry out performance based instrumental activities of daily living (IADL) in non-demented people with PD. As this test can be broken down into its multifactorial parts, using standard regression analyses they were further able to conclude that it is the ability to sequence in particular that is influential in the prediction of performance based IADL abilities in the non-demented PD population.

Both part A and part B of the Trail Making Test are very sensitive to the progressive cognitive decline found in dementia, with research indicating it is possible to differentiate dementing participants in the early stages of their disease from healthy controls on the basis of part A results only (Lezak et al., 2004).

Administrative errors can have a significant impact on a participant’s results on the Trail Making Test; hence accuracy and attention to detail when timing and pointing out errors to the subject are of utmost importance.

3.2.1.5 Stroop Test

As outlined in Strauss et al. (2006), the purpose of the Stroop test is to assess an individual’s ability to maintain focus on a specific goal and to suppress a habitual response in favour of a response that is less familiar to them. Originally developed as an assessment by Stroop (1935), all subsequent versions of the test have maintained its focus on measuring selective attention and cognitive flexibility, despite varying slightly in their formats.

The Victoria Stroop Test (VST; Regard, 1981) is a brief, commercially available version of the Stroop format. In contrast to several other version of the test, the VST has a much smaller number of items per condition (24, as opposed to some tests that include as many as 112). There is evidence to suggest that this shorter test
duration may be preferable for identifying individuals who have difficulties with the task as it prevents the extended practice inherent in version of the test that have upwards of 100 items (Strauss et al., 2006).

The VST required three cards (21.5x14cm), each containing six rows of four items. The VST is available for purchase, however it also exists in the public domain and instructions are readily available for constructing the stimulus material. This practice is permitted by the developer.

In part one (Dots) of the VST, individuals are asked to name aloud the colour of the 24 dots printed on the stimulus card (in red, blue, green & yellow). They are instructed to complete this task as quickly as possible. In part two (Words) common words are used instead of dots, and individuals are instructed to name the colour of the ink the word is printed in and to disregard the word itself. Part three (Colors) is similar to the first two parts, however the stimuli on the cards in this instance are the colour names (“red”, “blue”, “green”, “yellow”) printed in an ink colour that never matches (ie. “red” printed in green ink). Again, individuals are instructed to disregard the written word and to name the colour the word is printed in (Strauss et al., 2006). This final task requires inhibition of a habitual response, and maintained focus on a particular instruction, or goal. Time taken to complete each task, as well as any errors made, are recorded and used for scoring purposes. Spontaneously self-corrected errors are marked correct (Regard, 1981). Scaled scores and percentiles can be calculated for time taken and errors. An interference score can also be calculated. Initial normative data for the VST was derived from 272 healthy adults aged 18-94.

Neuroimaging studies have repeatedly shown that the frontal lobes are most consistently activated during Stroop administration. Focal frontal lesion studies have
supported this finding, with people tending towards poorer than normal interference results. However, while the frontal lobes appear to play a crucial role, other neuroanatomical regions have also been implicated, such as the hippocampus, the inferior temporal and parietal cortices, the caudate nuceli, and a number of neocortical regions (Strauss et al., 2006).

With regard to measuring cognitive decline, increased Stroop interference has been associated with dementia diagnoses. In addition to this, Kramer, Reed, Mungas, Weiner, and Chui, (2002) reported increased interference effects in people with subcortical infarcts.

Colour blindness and visual acuity can preclude use of this assessment as it relies upon the ability to read quickly and accurately discriminate colours.

3.2.1.6 National Adult Reading Test (NART; Nelson, 1982)

Pre-morbid intelligence is an estimate of an individual's intellectual ability prior to a disruption in cognitive functioning (Crawford, Parker, & Besson, 1988).

Observation of people with dementia led to the discovery that reading ability remains well preserved until well into the dementing process. Consequently, this information, along with the fact that reading ability is linked to general intellectual functioning in a normal adult population, led to the theory that oral reading ability could be used to assess prior intellectual functioning (Lucas, Carstairs, & Shores, 2003). Further research in the area has expanded this theory to include other forms of injury or illness.

The NART was initially developed in the United Kingdom as a measure of pre-morbid intelligence and is comprised of fifty irregular words that individual's must read and then pronounce aloud to the examiner (Lezak et al., 2004). These
words are predominantly short and of irregular pronunciation. For a short period following the development of this tool, it was criticised for questionable validity ratings however, it has since been widely researched and found to be an acceptable measure for estimating pre-morbid intelligence under a range of conditions, including alcoholic dementia, closed head injury, multi-infarct dementia, PD, and, most accurately, in mild to moderate dementia of the Alzheimer’s type (Crawford, Deary, Starr & Whalley, 2001).

NART error scores, obtained by calculating the number of words pronounced incorrectly, can be used to predict full scale intelligence (FSIQ), as well as performance IQ and verbal IQ, while the discrepancy tables can then be used to provide information on the extent of intellectual deterioration. A positive predicted versus obtained discrepancy (found by comparing NART estimates of predicted FSIQ to post injury measures of current FSIQ derived using the WAIS-III or Stanford Binet intelligence tests) indicates that the person was functioning at a higher level prior to their injury or disease on-set. The greater this positive discrepancy is, the more likely it is that damage has occurred (Lezak et al., 2004).

The irregular words used in this assessment are those that violate grapheme–phoneme correspondence rules. Prior exposure to the word is essential as individuals cannot use their current cognitive resources to correctly pronounce the words.

It is important to note that there are some limitations in the ways that the NART can be employed. These assessments are not appropriate for people with reading disorders, visual acuity deficits, language disorders (including severe dementia), and individuals who have English as their second language, although various countries have developed their own versions, such as the Swedish NART and the AusNART.
For ease of administration and scoring accuracy it is vital that the examiner is familiar with the correct pronunciation of each word, although cheat sheets are available to use as a guide. In addition to this, some researchers have found that the difficulty of some of the words can discourage people, which can be problematic for rapport development in an ongoing assessments and rehabilitation arrangement.

3.2.2 Assessment of Affective Symptoms

Non-motor symptoms of anxiety and depression are common in PD populations, with reviews suggesting as many as 40% of people with PD experience substantial levels of anxiety (Amini & Strafella, 2013; Leentjens et al., 2011) and 40-50% experience substantial levels of depression (Dobkin et al., 2012; Schrag et al., 2007) over the course of the disease. Symptoms of anxiety in PD have been associated with motor symptom presentation profiles, with increased subjective motor symptoms, more severe gait disturbances and dyskinesias, freezing, and on/off motor fluctuations all predictive of higher levels of anxiety (Leentjens, 2011). Likewise, symptoms of depression have been related to perception of motor symptoms (Dobkin et al., 2012), and can be a major determinant of health related quality of life, as well as having a significant impact upon cognitive functioning, ability to carry out functional activities of daily living, and caregiver quality of life (Schrag et al., 2007).

It can be difficult to accurately assess anxiety and depression in PD populations due to the overlap of some key symptoms and the complications associated with conducting mood assessments in individuals experiencing cognitive decline or dementia.
3.2.2.1 Hospital Anxiety and Depression Scale (HADS; Zigmond & Snaith, 1983)

The HADS is a fourteen item, two factor, self-rating questionnaire designed specifically to assess for the existence of anxiety disorders and depression symptoms among non-psychiatric patients. In both clinical and research settings, the HADS is one of the more commonly used anxiety and depression scales in PD. It is generally regarded as an appropriate tool given its creators were careful to exclude all symptoms of anxiety and depression that also relate to physical disorders, such as fatigue, headaches, insomnia, and dizziness (Bjelland, Dahl, Tangen Haug, & Necklemann, 2002).

Bjelland et al.’s 2002 updated review of the HADS concluded it performs well when assessing symptom severity and caseness of anxiety disorders and depression across a range of populations including somatic, psychiatric and primary care patients, as well as in the general population. Rodriguez-Blazquez et al. (2009, p. 519), in their study examining the psychometric properties of the HADS within a PD population, also concluded it to be “an acceptable, consistent, valid, precise, and potentially responsive scale for use in PD.”

However, within PD populations specifically, questions have been raised over the ability of the HADS to differentiate severe depression (Schrag et al., 2007), as well as over its construct validity as a tool for examining anxiety (Leentjens et al., 2011).
CHAPTER FOUR

Research Rationale

Parkinson’s disease is a complex degenerative neurological disorder with variable onset, severity, and progression profiles. At present it is estimated that 1% of people aged over 60 are affected by the disorder (Fritsch et al., 2012), and as life expectancies increase, PD is set to become a significant global health issue in coming decades.

While it has been postulated that a link between motor symptom severity, initial motor symptom onset and subsequent cognitive decline exists in PD, the results of a growing number of studies into the phenomenon have been equivocal and, at times, contradictory. It is also possible that motor symptom severity plays an integral role in the traditional reporting of symptoms of anxiety and depression as measured by two factor self-report scales such as the Hospital Anxiety and Depression Scale (HADS; Zigmond & Snaith, 1983). Due to the nature of the disease, methodological inconsistencies in the current research body are common and all researchers have stated that additional investigations in the area are required before more definitive conclusions can be reached.

Categorically establishing, and then understanding, the exact nature of this potential motor-non motor symptom link could enable treating physicians to better prepare people with PD and their families for what is to come as their disease progresses. Additional benefits of an increased understanding of this link would also include;
• The adaptation of existing, or the development of new treatment interventions for both motor and non-motor symptoms.

• Increasing patient quality of life through better understanding and preparedness.

• Establishing a better understanding of the pathophysiological processes involved in non-motor symptom development.

• Identifying existing (or developing new) anxiety and depression symptom measurement scales that can be used in a PD population without the patient’s current level of motor functioning confounding the results.

Study 1 of this thesis, presented in Chapter Five, further investigates the significance of motor symptom severity on cognitive functioning. In addition to this, regression analyses are used to examine which factors play an important role in predicting cognitive performance. Study 2 (Chapter Six) moves from there into a closer examination of motor functioning, examining the effect of motor symptom onset lateralisation on cognitive functioning. Study 3 (presented in Chapter Seven) examines the effects of motor symptom presentation on HADS result using both the traditional two-factor approach and a more recent three-factor approach.
CHAPTER FIVE

STUDY 1: Motor symptom severity and cognitive functioning

Parkinson’s disease, the second most common neurodegenerative disorder after Alzheimer’s disease (AD; Meireles & Massano, 2012), is characterised by its cardinal motor symptoms; tremor and rigidity/bradykinesia (Gazewood et al., 2013). Despite the long held view that PD was a disorder of motor functioning only and did not cause cognitive decline in those diagnosed, more recent research has shown this notion to be unequivocally false. PD is now viewed as a multisystem disease also affecting cognitive and behavioural domains, even in early disease stages (Mak et al., 2013).

As with motor symptoms, the experience of cognitive symptoms in PD can differ significantly from person to person. Generally, it is accepted that people with PD will experience a cognitive decline pattern that differs from the decline typically seen in AD, with domains such as attention, executive functioning, and visuospatial skills more likely to be affected, while memory encoding and language remain relatively intact (Poewe et al., 2008).

Although a number of factors have been identified as potentially increasing risk for cognitive impairment in PD, no definitive conclusions have been reached and there is still much to learn about its complicated nature. For a more detailed review of this topic, see Chapter One.

Motor symptom severity has emerged as perhaps the preponderant risk factor for subsequent cognitive decline in PD, however as outlined in a recent review article by Palavra et al., (2013), there is still little in the way of consensus regarding
its role. In addition to this, a literature search revealed there is no research to date that examines the potential relationship between motor symptom severity and specific cognitive domains such as memory, executive functioning, attention, language, and emotional functioning, with broad screening measures such as the MMSE typically used to assess cognitive functioning (Palavra, 2013).

There are a number of ways in which motor symptom severity can be determined, with measures such as grip strength, manual dexterity and motor speed having been identified as particularly useful (Strauss et al., 2006). Despite this, little research exists on the degree to which impairment across each of these components, individually and as a group, is able to predict cognitive decline, or whether additional factors such as age, education, pre-morbid functioning and disease duration also play important roles (Palavra et al., 2013). Identifying assessment options that are more effective at predicting cognitive decline is useful for clinicians working with people with PD for several reasons; Firstly, as fatigue and pain are both common symptoms in PD (Aarsland & Kurs, 2010), single measures to examine different aspects of the disease are helpful for reducing assessment length; Secondly, identifying key prognostic variables allows clinicians to gather vital background data in a way that is both economically and professionally feasible.

The ability to not only identify but potentially predict likely cognitive decline for people diagnosed with PD will significantly assist with tasks such as determining pharmacological treatment regimes, planning cognitive interventions, establishing care plans for later life, and helping to improve quality of life and reduce carer burden.
5.1 Aims and Hypothesis

The aim of the current study was to use exploratory techniques to investigate the role of motor functioning (as determined by grip strength, manual dexterity, & motor speed) on a variety of cognitive domains in participants diagnosed with idiopathic Parkinson’s disease.

The hypothesis for this study was:

- Decreased motor functioning will be predictive of a poorer cognitive functioning profile.

An additional aim for this study was to use stepwise regression analysis (Tabachnick & Fidell, 2013) to examine the degree to which various motor functioning measures predict cognitive decline when compared to demographic variables such as age, sex, years of education, pre-morbid functioning and disease duration.

5.2 Method

5.2.1 Participants

Participants (n = 88) were recruited from the Royal Hobart Hospital Parkinson’s disease outpatient clinics. All participants had received a diagnosis of Idiopathic Parkinson’s disease from their neurologist or geriatrician. Participants were excluded on the basis of prior head-injury or other neurological illness as well as on the basis of incomplete assessment protocols (reasons for incomplete protocols include administration errors or oversights and time restrictions put in place by participants). Major psychiatric disorder was also an initial exclusion criterion; however none of the recruited participants had a relevant co-morbid diagnosis; thus no exclusions were made on this basis. Using a composite motor functioning
discrepancy score, obtained by adding age and gender corrected discrepancy scores together for the three key motor functioning measures (motor speed, grip strength as measured by the hand dynamometer, & manual dexterity as measured by the Finger Tapping Test), all included participants (n = 50) were then divided into two groups using a median split; higher functioning (discrepancy scores between -26 & 38) and lower functioning (discrepancy scores between -27 & -61). Ethical approval was obtained from the Tasmanian Health and Medical Research Ethics Committee (approval number: H0010104; see Appendix A1).

5.2.2 Materials

The individual assessments comprising the neuropsychological battery used in this research were selected based on their empirical sensitivity to cognitive functions known to be impaired in Parkinson’s disease (see Chapter Three).

- The Hospital Anxiety and Depression Scale (HADS; Zigmond & Snaith, 1983) was used to detect possible symptoms of anxiety and depression. This fourteen item, two factor scale was originally developed for use in non-psychiatric populations, and was carefully designed so as not to include symptoms of anxiety and depression that also relate to physical conditions (such as dizziness, insomnia, & fatigue; Bjelland et al., 2002).

- The Repeatable Battery for the Assessment of Neuropsychological Status (RBANS; Randolph, 1998) was used to assess cognitive functioning across a range of areas; immediate memory, language, attention and delayed memory, and visuospatial/constructional. All twelve subtests were administered and scored
according to the administration manual. Raw scores were used to obtain age corrected standard scores for the five individual indexes, as well as an age corrected overall standard score, and age corrected discrepancy scores for each of the twelve individual subtests.

- The digit span subtest from the *Wechsler Adult Intelligence Scale Third Edition* (WAIS III; Wechsler, 1997) was administered due to its digits backwards component, a feature that is not a part of the digit span subtest of the RBANS. Standard instructions were used for administration. Raw scores for both the forwards and backwards components were recorded and the WAIS III manual was used to calculate an overall standard score.

- The *Controlled Oral Word Association Test* was used to assess verbal fluency. The letters used were F, A, and S. Each participant’s total score was adjusted for age and education and converted to a standard score and a percentile.

- Part A and Part B of the *Trail Making Test* were used to assess scanning and visuo-motor tracking, divided attention and cognitive flexibility. Both test trials were timed, with the times then converted to scaled scores and percentiles using the norms established by Tombaugh (2004).

- The *Brixton Spatial Anticipation Test* (Burgess & Shallice, 1997) was used to assess concept formation and rule detection. Scaled scores were used for the analysis.
• The three part *Victoria Stroop Test* (Regard, 1981; reviewed in Strauss et al., 2006) was used to assess mental flexibility, directed attention and concentration. Spontaneous self-corrections were not scored as errors as per the scoring instructions (Strauss et al., 2006). Scaled scores for each of the three parts were used for the analysis, as well as the cumulative percentile rank for errors made.

• The two part *Speed of Information Processing* subtest from the *Brain Injury Rehabilitation Trust Memory and Information Processing Battery* (Coughlan, Oddy, & Crawford, 2007) was used to assess information processing speed. In the first task participants were instructed to examine a row of five numbers, decide which number was the second highest, and cross it out. They were told to work their way down the page repeating this process without skipping any rows. If they completed a full column, they were to start again at the top of the page in column two, and then column three if necessary and to continue until they were instructed to stop. They were told to work as quickly and as accurately as possible. They were given four minutes to complete this first task. They were given several examples to practice on first. The second test, a test of motor speed, participants were instructed to examine a row of dashes that also contained the number 11 (eg. - - - 11 -) and to put a cross only through the number. The 11s were distributed randomly in each row and participants were instructed to quickly and accurately work their way down the page without skipping any. This subtest is timed, and at twenty five seconds participants are instructed to stop. A standard practice trial was completed prior to attempting the test.
• The *National Adult Reading Test* (NART; Nelson, 1982) was used to assess pre-morbid intellectual functioning. Participants were asked to read aloud down a list of fifty phonetically irregular words presented in order of increasing difficulty. Errors were recorded and used to calculate a premorbid WAIS-III FSIQ estimate for each participant.

• A *hand dynamometer* was used to assess grip and muscle strength (Dodrill, 1978). Starting with the participant’s dominant hand, four alternating trials were conducted (two dominant & two non-dominant). Participants were instructed on how to accurately hold the device, and measurements were recorded for each trial. If scores for the two trials varied by more than five kilograms, an additional trial was administered. A discrepancy score for both the dominant and non-dominant hand was calculated by subtracting the age and gender appropriate expected mean score from the participant’s actual mean score (Spreen & Strauss, 1998).

The *Finger Tapping Test* (Halstead-Reitan Neuropsychological Test Battery; Reitan & Wolfson, 1993) was used to assess motor control, speed and degree of dysfunction. Starting with the participant’s dominant hand, ten alternating trials (five dominant & five non-dominant) were administered, with total finger taps per each ten second trial recorded. Two additional trials were conducted if the total fingers taps for each hand varied by more five taps per trial. A discrepancy score for both the dominant and non-dominant hand was calculated by subtracting the age and gender appropriate expected mean score from the participant’s actual mean score (Ruff & Parker, 1993).
5.2.3 Procedure

All participants provided written informed consent and attended a standardised assessment session largely carried out at the Royal Hobart Hospital (see Appendix A2 & A3 for copies of the Information Sheet & Consent Forms used for this research). In home assessment sessions were offered for convenience if necessary. The tests outlined above were administered by trained research assistants (post-graduate psychology students from the University of Tasmania) as part of a slightly larger assessment battery. This battery also included questionnaires for the collection of general demographic information, disease specific information such as time since onset and side of motor symptom onset (see Appendix B1), life experience history, current medications, and anxiety and depression levels (HADS; Zigmond & Snaith, 1983). No payment was provided for participation in this research.

5.2.4 Design and Statistical Analyses

This quasi-experimental design employed independent samples t-tests and stepwise linear regression analyses (Tabachnick & Fidell, 2013) to examine the data.
5.4 Results

An independent samples t-test was used to assess the equality of the means between the two experimental motor functioning groups prior to further investigation.

Table 5.1

Descriptive Statistics and T-tests for the Two Motor Functioning Groups

<table>
<thead>
<tr>
<th></th>
<th>Lower (n =25, males=13)</th>
<th>Higher (n =25, males=9)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean SD</td>
<td>Mean SD</td>
</tr>
<tr>
<td>Age</td>
<td>70.80 9.241</td>
<td>66.48 10.936</td>
</tr>
<tr>
<td>Years of education</td>
<td>10.60 2.327</td>
<td>11.48 2.960</td>
</tr>
<tr>
<td>NART FSIQ</td>
<td>106.70 10.07</td>
<td>105.88 9.431</td>
</tr>
<tr>
<td>Years since PD dx</td>
<td>8.78 7.149</td>
<td>8.00 8.652</td>
</tr>
<tr>
<td>Anxiety</td>
<td>8.08 4.071</td>
<td>6.04 3.446</td>
</tr>
<tr>
<td>Depression</td>
<td>5.92 4.377</td>
<td>4.76 3.382</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>t</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.523</td>
<td>ns</td>
</tr>
<tr>
<td>Years of education</td>
<td>-1.169</td>
<td>ns</td>
</tr>
<tr>
<td>NART FSIQ</td>
<td>0.347</td>
<td>ns</td>
</tr>
<tr>
<td>Years since PD dx</td>
<td>0.297</td>
<td>ns</td>
</tr>
<tr>
<td>Anxiety</td>
<td>1.912</td>
<td>ns</td>
</tr>
<tr>
<td>Depression</td>
<td>1.048</td>
<td>ns</td>
</tr>
</tbody>
</table>

Note: lower = lower age/gender corrected motor functioning; higher = higher age/gender corrected motor functioning.

As Table 5.1 indicates, there were no significant between-groups differences for age, years of education, pre-morbid FSIQ as measured by the National Adult Reading Test (NART; Nelson, 1982), time elapsed (in years) since PD diagnosis, anxiety or depression. An additional independent samples t-test showed females (\(M = -13.55, \ SD = 25.83\)) and males (\(M = -25.06, \ SD = 20.79\)) did not differ significantly on measures of motor functioning, \(t(48) = 1.702, \ p = .095\) (ns). Due to this non-significant result, males and females were combined for all subsequent motor symptom severity analyses.

Standardised residuals were calculated and used to detect outliers as per Tabachnick and Fidell’s (2013) criteria. Results of this analysis indicated there were no outliers and consequently no participants were excluded on this basis.
Additional independent samples t-tests were used to compare cognitive functioning on the RBANS across the two motor functioning groups. Results for the RBANS total and the five RBANS indices have been displayed in Table 5.2. The full output is provided in Appendix C1a. Age adjusted standard scores were calculated for each participant and used for analysis.

Table 5.2

<table>
<thead>
<tr>
<th>RBANS Scale</th>
<th>Lower (n=25)</th>
<th>Higher (n=25)</th>
<th>t</th>
<th>Cohen's d</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
<td>SD</td>
</tr>
<tr>
<td>Total</td>
<td>6.60</td>
<td>3.08</td>
<td>8.71</td>
<td>2.84</td>
</tr>
<tr>
<td>Imm. Memory</td>
<td>5.04</td>
<td>3.22</td>
<td>6.68</td>
<td>3.56</td>
</tr>
<tr>
<td>Visuospatial/Cons</td>
<td>9.04</td>
<td>3.92</td>
<td>10.56</td>
<td>3.07</td>
</tr>
<tr>
<td>Language</td>
<td>8.92</td>
<td>3.10</td>
<td>9.79</td>
<td>1.96</td>
</tr>
<tr>
<td>Attention</td>
<td>6.96</td>
<td>3.60</td>
<td>9.52</td>
<td>2.90</td>
</tr>
<tr>
<td>Del. Memory</td>
<td>6.68</td>
<td>4.05</td>
<td>8.16</td>
<td>3.89</td>
</tr>
</tbody>
</table>

*n = 24
* p <.05, ** p <.01

Note: lower: lower age/gender corrected motor functioning, higher: higher age/gender corrected motor functioning.

The t-test for the Immediate Memory Index was only trending towards being significant (p = .094).

Discrepancy scores for individual RBANS subtests were calculated by subtracting the age adjusted expected score (obtained from the manual; Randolph, 1998) from each participant’s actual score. Negative values indicate the participant performed at a level below what would typically be expected for an individual of their age, while positive values indicate performance at or above what would be expected for an individual of their age. Table 5.3 contains the independent samples t-test results and Cohen’s d values for the two motor functioning groups for age corrected discrepancy scores on all twelve RBANS subtests. All results are in the
predicted direction with the lower motor functioning group performing consistently more poorly (see Figure 5.1 for additional illustration of these results).

Table 5.3

*Independent Samples T-test Results and Cohen’s d Effect Sizes for the RBANS Subtest Discrepancy Scores*

<table>
<thead>
<tr>
<th>RBANS Subtest</th>
<th>Lower (n=25)</th>
<th></th>
<th>Higher (n=25)</th>
<th></th>
<th>t</th>
<th>Cohen's d</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
<td>SD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>List Learning</td>
<td>-7.12</td>
<td>5.809</td>
<td>-5.04</td>
<td>6.065</td>
<td>-1.234</td>
<td></td>
</tr>
<tr>
<td>Story Mem.</td>
<td>-5.17</td>
<td>3.567</td>
<td>-2.96</td>
<td>4.590</td>
<td>-1.900</td>
<td></td>
</tr>
<tr>
<td>Figure Copy</td>
<td>-0.70</td>
<td>3.150</td>
<td>-0.144</td>
<td>2.838</td>
<td>-0.660</td>
<td></td>
</tr>
<tr>
<td>Line Orient.</td>
<td>-0.64</td>
<td>3.710</td>
<td>1.15</td>
<td>2.660</td>
<td>-1.960</td>
<td></td>
</tr>
<tr>
<td>Picture Naming</td>
<td>0.02</td>
<td>1.186</td>
<td>0.168</td>
<td>0.593</td>
<td>-0.558</td>
<td></td>
</tr>
<tr>
<td>Semantic Fluency</td>
<td>-1.50</td>
<td>5.365</td>
<td>0.53</td>
<td>4.318</td>
<td>-1.449</td>
<td></td>
</tr>
<tr>
<td>Digit Span</td>
<td>1.77</td>
<td>3.974</td>
<td>2.49</td>
<td>4.539</td>
<td>-0.597</td>
<td></td>
</tr>
<tr>
<td>Coding</td>
<td>-11.92</td>
<td>12.170</td>
<td>-1.69</td>
<td>9.300</td>
<td>-3.340**</td>
<td>-0.944</td>
</tr>
<tr>
<td>List Recall</td>
<td>-2.04</td>
<td>2.251</td>
<td>-0.73</td>
<td>2.243</td>
<td>-1.027</td>
<td></td>
</tr>
<tr>
<td>List Recognition</td>
<td>-1.44</td>
<td>2.328</td>
<td>-0.75</td>
<td>1.850</td>
<td>-1.164</td>
<td></td>
</tr>
<tr>
<td>Story Recall</td>
<td>-3.09</td>
<td>2.640</td>
<td>-0.73</td>
<td>2.240</td>
<td>-3.400**</td>
<td>-0.963</td>
</tr>
<tr>
<td>Figure Recall</td>
<td>-2.40</td>
<td>4.600</td>
<td>0.12</td>
<td>3.280</td>
<td>-2.22*</td>
<td>-0.301</td>
</tr>
</tbody>
</table>

* p < .05, ** p < .01

Note: lower: lower age/gender corrected motor functioning, higher: higher age/gender corrected motor functioning.

In addition to the significant results detailed in the table above, the Story Memory subtest ($p = .064$) and the Line Orientation subtest ($p = .056$) were both trending strongly towards significance.
Independent samples t-tests were also conducted for additional cognitive measures. Significant results and results trending towards being significant have been displayed in Table 5.4. A copy of the full output can be viewed in Appendix C1a.
Table 5.4

*Independent Samples T-test Results and Cohen’s d Effect Sizes for Additional Cognitive Measures*

<table>
<thead>
<tr>
<th></th>
<th>Higher (n = 25)</th>
<th>Lower (n = 25)</th>
<th>t</th>
<th>Cohen’s d</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
<td>SD</td>
</tr>
<tr>
<td>Brixton</td>
<td>2.25</td>
<td>1.567</td>
<td>4.68</td>
<td>2.015</td>
</tr>
<tr>
<td>BMIPB Proc. Speed</td>
<td>3.32</td>
<td>2.719</td>
<td>8.30b</td>
<td>2.089</td>
</tr>
<tr>
<td>Trails A</td>
<td>6.46</td>
<td>3.859</td>
<td>8.80</td>
<td>3.317</td>
</tr>
<tr>
<td>Trails B</td>
<td>6.30c</td>
<td>3.596</td>
<td>8.28</td>
<td>3.260</td>
</tr>
<tr>
<td>Stroop Dots</td>
<td>7.13a</td>
<td>2.419</td>
<td>10.88</td>
<td>2.868</td>
</tr>
<tr>
<td>Stroop Words</td>
<td>7.21a</td>
<td>2.670</td>
<td>9.44</td>
<td>2.840</td>
</tr>
<tr>
<td>Stroop Colors</td>
<td>9.04a</td>
<td>3.150</td>
<td>11.76</td>
<td>3.200</td>
</tr>
</tbody>
</table>

* n = 24, b n = 23, c n = 21

* p < .05, ** p < .01, *** p < .001

note: higher age/gender corrected motor functioning and lower age/gender corrected motor functioning.

The difference between the two groups on the Trails B task also showed a strong trend towards significance (p = .061). Mean scaled score comparisons of the two motor functioning groups can be seen in Figure 5.2, and once again all results were in the predicted direction with the lower motor functioning group consistently performing more poorly.
Stepwise linear multiple regression analyses were used to investigate whether motor functioning measures predicted performance on various tasks across a number of cognitive domains. Step 1 of the regression analyses involved measures of motor speed, dominant and non-dominant grip strength (hand dynamometer), and dominant and non-dominant manual dexterity (Finger Tapping Test). The predictive capabilities of the additional demographic factors age, sex, disease duration, years of education and NART estimated FSIQ were also investigated in step 2. $F$ scores and $p$ values for each of the final models can be seen in Table 5.5 (see Appendix C1b for complete statistical output), while Table 5.6 shows the unstandardized beta coefficients and constant values.
Table 5.5

*Final Model Regression Coefficients and p Values for all Subtests*

<table>
<thead>
<tr>
<th>Predicted Variable</th>
<th>Model</th>
<th>$R$</th>
<th>$R^2$</th>
<th>$F$</th>
<th>$p$</th>
</tr>
</thead>
<tbody>
<tr>
<td>RBANS</td>
<td>Total</td>
<td>3. Motor speed, NART, YoE</td>
<td>0.554</td>
<td>0.307</td>
<td>6.791</td>
</tr>
<tr>
<td></td>
<td>Imm Mem</td>
<td>2. NART, YoE</td>
<td>0.527</td>
<td>0.278</td>
<td>9.041</td>
</tr>
<tr>
<td></td>
<td>Visuospatial/Cons</td>
<td>2. Non-dom dyna., disease duration</td>
<td>0.309</td>
<td>0.095</td>
<td>2.477</td>
</tr>
<tr>
<td></td>
<td>Language</td>
<td>2. Non-dom dyna., YoE</td>
<td>0.392</td>
<td>0.154</td>
<td>4.276</td>
</tr>
<tr>
<td></td>
<td>Attention</td>
<td>3. Motor speed, non-dom finger tap, NART</td>
<td>0.576</td>
<td>0.332</td>
<td>7.623</td>
</tr>
<tr>
<td></td>
<td>Delayed Mem</td>
<td>3. Motor speed, YoE, sex</td>
<td>0.507</td>
<td>0.257</td>
<td>5.314</td>
</tr>
<tr>
<td></td>
<td>List Learning</td>
<td>3. YoE, NART, sex</td>
<td>0.594</td>
<td>0.310</td>
<td>8.355</td>
</tr>
<tr>
<td></td>
<td>Story Memory</td>
<td>2. YoE, NART</td>
<td>0.460</td>
<td>0.212</td>
<td>6.305</td>
</tr>
<tr>
<td></td>
<td>Figure Copy</td>
<td>2. Dom dynamometer, sex</td>
<td>0.376</td>
<td>0.142</td>
<td>3.877</td>
</tr>
<tr>
<td></td>
<td>Line Orient.</td>
<td>3. Non-dom finger tap, YoE, disease duration</td>
<td>0.483</td>
<td>0.233</td>
<td>4.665</td>
</tr>
<tr>
<td></td>
<td>Picture Naming</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Semantic Fluency</td>
<td>2. Motor speed, YoE</td>
<td>0.401</td>
<td>0.160</td>
<td>4.492</td>
</tr>
<tr>
<td></td>
<td>Digit Span</td>
<td>2. YoE, NART</td>
<td>0.526</td>
<td>0.277</td>
<td>9.010</td>
</tr>
<tr>
<td></td>
<td>Coding</td>
<td>4. Motor speed, non-dom finger tap, sex, YoE</td>
<td>0.623</td>
<td>0.389</td>
<td>7.149</td>
</tr>
<tr>
<td></td>
<td>List Recall</td>
<td>2. YoE, sex</td>
<td>0.478</td>
<td>0.228</td>
<td>6.953</td>
</tr>
<tr>
<td></td>
<td>List Recognition</td>
<td>3. Motor speed, YoE, sex</td>
<td>0.499</td>
<td>0.249</td>
<td>5.076</td>
</tr>
<tr>
<td></td>
<td>Story Recall</td>
<td>2. Motor speed, YoE</td>
<td>0.573</td>
<td>0.328</td>
<td>11.459</td>
</tr>
<tr>
<td></td>
<td>Figure Recall</td>
<td>2. Motor speed, NART</td>
<td>0.405</td>
<td>0.104</td>
<td>4.605</td>
</tr>
<tr>
<td>OTHER</td>
<td>FAS</td>
<td>1. NART</td>
<td>0.348</td>
<td>0.121</td>
<td>6.615</td>
</tr>
<tr>
<td></td>
<td>Brixton SAT</td>
<td>3. Motor speed, YoE, sex</td>
<td>0.584</td>
<td>0.340</td>
<td>7.916</td>
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<tr>
<td></td>
<td>WAIS Digit Span</td>
<td>2. Dominant finger tap, NART</td>
<td>0.469</td>
<td>0.220</td>
<td>6.614</td>
</tr>
<tr>
<td></td>
<td>Stroop Dots</td>
<td>2. Motor speed, NART</td>
<td>0.586</td>
<td>0.344</td>
<td>12.319</td>
</tr>
<tr>
<td></td>
<td>Stroop Words</td>
<td>2. Motor speed, NART</td>
<td>0.614</td>
<td>0.377</td>
<td>14.200</td>
</tr>
<tr>
<td></td>
<td>Stroop Colors</td>
<td>4. Motor speed, NART, age, sex</td>
<td>0.629</td>
<td>0.395</td>
<td>7.358</td>
</tr>
<tr>
<td></td>
<td>Stroop Interference</td>
<td>2. Sex, age</td>
<td>0.336</td>
<td>0.113</td>
<td>2.987</td>
</tr>
<tr>
<td></td>
<td>Trails A</td>
<td>2. Motor speed, non-dom finger tap</td>
<td>0.394</td>
<td>0.156</td>
<td>4.331</td>
</tr>
<tr>
<td></td>
<td>Trails B</td>
<td>2. Motor speed, sex</td>
<td>0.316</td>
<td>0.100</td>
<td>2.558</td>
</tr>
</tbody>
</table>

YoE = Years of education
Table 5.6

**Unstandardised Beta Coefficients and Constant Values for all RBANS Measures**

<table>
<thead>
<tr>
<th>Predicted Variable</th>
<th>Predictor</th>
<th>B</th>
<th>Constant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>Motor speed</td>
<td>0.065</td>
<td></td>
</tr>
<tr>
<td></td>
<td>NART</td>
<td>0.090</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Years of education</td>
<td>0.298</td>
<td>-8.360</td>
</tr>
<tr>
<td>Imm Memory</td>
<td>NART</td>
<td>0.119</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Years of education</td>
<td>0.374</td>
<td>-10.971</td>
</tr>
<tr>
<td>Visuospatial/Cons</td>
<td>Non-dominant dynamometer</td>
<td>0.100</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Disease duration</td>
<td>-0.125</td>
<td>10.831</td>
</tr>
<tr>
<td>Language</td>
<td>Non-dominant dynamometer</td>
<td>0.102</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Years of education</td>
<td>0.333</td>
<td>5.859</td>
</tr>
<tr>
<td>Attention</td>
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<td>Non-dominant finger tap</td>
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<td>Years of education</td>
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<td>Sex</td>
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<td>NART</td>
<td>0.127</td>
<td>-19.945</td>
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Table 5.7

*Unstandardised Beta Coefficients and Constant Values for all Additional Cognitive Measures*

<table>
<thead>
<tr>
<th>Predicted Variable</th>
<th>Predictor</th>
<th>$B$</th>
<th>Constant</th>
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</thead>
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<tr>
<td>FAS</td>
<td>NART</td>
<td>0.121</td>
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<tr>
<td>Brixton SAT</td>
<td>Motor speed</td>
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<tr>
<td></td>
<td>Years of education</td>
<td>0.231</td>
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<td></td>
<td>Sex</td>
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<td>-3.852</td>
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<td>WAIS Digit Span</td>
<td>Dominant finger tap</td>
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<tr>
<td></td>
<td>NART</td>
<td>0.116</td>
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</tr>
<tr>
<td>Stroop Dots</td>
<td>Motor speed</td>
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<tr>
<td></td>
<td>NART</td>
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<td>Stroop Words</td>
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<td>NART</td>
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<td>NART</td>
<td>0.092</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Age</td>
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<td>Sex</td>
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<td>Non-dominant finger tap</td>
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<tr>
<td></td>
<td>Sex</td>
<td>-9.464</td>
<td>95.977</td>
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</table>
5.5 Discussion

This study examined the relationship between motor functioning and cognition in people diagnosed with idiopathic PD. In addition to this, regression analysis was used to identify any motor functions and other demographic variables capable of predicting performance on a range of tasks across a number of cognitive domains.

5.5.1 Motor Symptom Severity and Cognitive Functioning

Although there is some previous research examining the relationship between motor symptom severity and cognitive functioning, results have typically been inconclusive, with the majority of researchers recommending additional studies be undertaken. This study investigated the hypothesis that participants with a lower current motor functioning levels would perform more poorly on cognitive tasks than participants with comparatively higher current motor functioning levels (as determined by age/gender corrected discrepancy scores on tests of motor speed, grip strength, & manual dexterity).

No significant between groups differences on any demographic variables, including age, pre-morbid intellectual functioning, disease duration, psychological functioning, or years of education were noted. However, participants in the lower motor functioning group achieved mean scores that were below those achieved by the higher motor functioning group across every cognitive index, subtest and individual assessment included in this research. This difference between the mean scores achieved by the two groups reached significance ($p < .05$) for the RBANS Total. This global cognitive functioning score is made up of results from a range of tasks across various domains including immediate and delayed memory, attention,
language and visuospatial/constructional ability. More specifically, significant differences were found on tasks from this battery requiring attention (Coding, $p < .01$) and delayed verbal and visual memory (Story Recall, $p < .01$; Figure Recall, $p < .05$), while results trending towards significance included the Immediate Memory Index ($p = .094$), as well as the Story Memory ($p = .064$) and Line Orientation ($p = .056$) subtests. Caution needs to be taken when interpreting the significant result found for the Coding subtest of the RBANS as this measure relies heavily on motor performance. It is likely that a portion of the difference in mean scores between the two groups can be attributed to motor symptom severity, as opposed to purely differentiating between the groups based on attention abilities.

The differences between the groups for the three related tasks, List Learning, List Recall and List Recognition, were not significant. This result reflects what is currently understood of cognitive decline in PD populations and its tendency towards affecting executive functioning and visuospatial skills, while leaving memory and language skills relatively unimpaired, particularly when compared to other neurodegenerative disorders such as Alzheimer’s disease (Poewe et al., 2008). The significant results found for the delayed verbal and visual memory tasks of Story Recall and Figure Recall are more difficult to explain, although there is also research available that suggests people with PD may not be completely spared memory deficits as previously believed. Katzen et al. (2006) compared healthy controls to people with PD across a number of cognitive domains and found that, while those with right side tremor onset did not cognitively differ from the healthy controls, the three other experimental groups (left side tremor onset, and left and right bradykinesia/rigidity onset) performed significantly more poorly on all cognitive
domains assessed. The discrepancies in these findings highlight the need for additional research.

The RBANS Picture Naming subtest failed to discriminate between the two groups, which may be reflective of the task’s lack of overall sensitivity to cognitive decline in Parkinson’s disease, with a large number of participants ($n = 39/50$) achieving a raw score of 10/10. An additional eight participants scored 9/10.

In addition to the RBANS, the group with lower motor functioning levels also performed significantly more poorly on several tasks of executive functioning, including concept formation as measured by the Brixton Spatial Anticipation Test ($p < .001$), which has no speed component and can be completed without need of any motor functioning abilities besides articulation. In addition to concept formation, the lower motor functioning group also performed more poorly on response generation and response inhibition as measured by the Stroop test ($p < .001$). As well as these significant results, Trails B (response generation, response inhibition & cognitive flexibility) was trending towards significance ($p = .061$). Executive functioning is one of the cognitive domains most consistently affected by the pathophysiology of Parkinson’s disease and a recent review by Dirnberger and Jahanshahi (2012) concluded that the worsening of motor symptoms is associated with poorer executive functioning. In a review of the relationship between the basal ganglia and the development of PD, Cools (1984) concluded that people with PD experience reduced ability to voluntarily shift between behaviour programs, are fully dependent on current available sensory information for shifting, and display manifestations of this deficit across both motor and cognitive domains, thus indicating the motor and non-motor symptoms of PD should not be regarded as separate entities. The results of the current study further support this finding.
5.5.2 Predictors of Cognitive Decline

The current study used stepwise multiple linear regression analysis in an attempt to identify potential predictors of cognitive decline. While the focus was primarily on different measures of motor functioning, additional demographic factors such as age, years of education, pre-morbid intellectual functioning and disease duration were included in the analysis at step two.

While several motor functioning measures featured in the regression models, motor speed, as assessed by the adjusted motor speed scaled score from the BMIPB, appears to be the most prominent factor. Fourteen of the twenty seven subtests analysed had this measure of motor speed as one of the key predictors. Even subtests that did not involve a timed component or the specific completion of any physical movements, such as the Brixton Spatial Anticipation Test and various RBANS subtests like Story Memory and List Recognition, had motor speed (as measured by the adjusted motor speed score from the BMIPB) playing a key role.

Previous research has singled out the importance of motor symptom type at disease onset when examining the relationship between motor symptoms and subsequent cognitive decline, with rigidity and/or bradykinesia at onset more strongly associated with greater levels of subsequent cognitive dysfunction than tremor at onset (Katzen, 2000). It is possible that motor speed scores in the current experiment have been significantly influenced by the presence of symptoms of rigidity and/or bradykinesia/hypokinesia and therefore its prominence in the regression analyses may be a reflection of this already established link with cognitive decline. The pathophysiology of bradykinesia is relatively well understood to be caused by a loss of nigrostriatal dopaminergic inputs. The result is disordered output from the basal ganglia to the thalamocortical pathways (MacKinnon & Rothwell,
While the exact pathophysiology of rigidity remains an area of debate, people with PD experiencing bradykinesia and/or hypokinesia typically exhibit a longer latency time before movements commence, take longer reaching optimum speed and force of movements, and their movements are more likely to be broken down into a series of smaller steps, requiring multiple bursts of movement to achieved the desired result (Santens et al., 2003). Despite less certainty regarding the pathophysiology of cognitive decline in PD, the importance of dopaminergic connections has been suggested (Chaudhuri & Schapiro, 2009; Cools, 1984).

Additional demographic variables that featured strongly in the regression models included years of education, NART full scale IQ scores, and sex. Regression coefficients suggest that increased years of education, higher pre-morbid functioning, and being female are all factors that are somewhat protective against the development of PD related cognitive decline. The identification of sex as a potential predictor was an interesting find in light of the non-significant difference (although weak trend, $p = .095$) between males and females in the first stage of the analysis. It may be possible that, despite similar current motor functioning levels, males are more likely to experience cognitive deficits. It is recommended that additional research be carried out in this area.

5.5.3 Limitations of the Current Study and Suggestions for Future Research

It is acknowledged that the number of variables included in the current study is quite large, resulting in reduced statistical power. This study has broadly examined the impact of motor functioning on a wide variety of cognitive domains and has developed a solid platform from which future research, with more a more targeted cognitive domain focus, can be based.
While each participant’s current level of motor functioning was calculated using standardised assessments and age/gender corrected norms, no additional motor functioning information was available from other sources for comparison; for example, the Unified Parkinson’s Disease Rating Scale (UPDRS). In addition to this, the relatively small sample size \((n = 50)\) meant it was not statistically feasible to divide the participants into more than two groups (lower current motor functioning & higher current motor functioning).

The current study did not differentiate between the types of motor symptoms (tremor versus rigidity/bradykinesia for example) experienced by each participant. There has been some previous research suggesting that motor symptom type may be an important factor when examining the relationship between motor functioning and cognition; however this information was not available from medical records for the current study. As a consequence it was not possible to include any analysis that examined this potential relationship. As some people will present at time of disease onset with one type of motor symptom (typically, but not always, tremor) but then gradually develop additional types of motor symptoms, future research into the significance of motor symptoms should seek to include type of motor symptom experienced, both at time of disease onset and at time of subsequent research based assessment.

Previous PD research has varied with regard to the use of a control group. The difficulty in determining what would make an appropriate control group in this instance (with participants ranging in age from 41 to 88) meant that it was decided not to use one. Instead, discrepancy scores were used whereby each individual participants result (where appropriate) was compared to the age/gender corrected
normative score or pre-morbid estimate available for that subtest. In this way, a quasi-control group was established.

As the current study was focussed on the examination of type of motor symptom at onset, the impact of symptom laterality was not examined. Previous research has identified symptom laterality at onset as potentially playing a predictive role in the type and severity of cognitive symptoms experienced as the PD progresses. This phenomenon is addressed in Study 2.
CHAPTER SIX

STUDY 2: Motor symptom onset laterality and its relationship with subsequent cognitive decline

As discussed previously, PD is a neurodegenerative disorder largely characterised by its cardinal motor symptoms, tremor and rigidity/bradykinesia. While motor impairment often progresses towards a bilateral presentation, typically the disease is first recognised when the patient is experiencing unilateral symptom onset. In addition to debilitating motor symptoms, people diagnosed with PD can expect to experience some degree of cognitive deterioration over the course of the disease. This can range from a mild cognitive impairment, all the way through to Parkinson’s disease dementia.

Findings from previous research (see Chapter Two for review) examining the relationship between motor symptom onset laterality and the type and severity of any subsequent cognitive decline in PD have been mixed and inconclusive. Much of the research already conducted in this area has used broad screening measures such as the MMSE and the DRS to assess cognitive decline with limited focus on individual cognitive domains (Cooper, 2009).

Research exists both in support of and against the notion of a meaningful relationship between motor symptom onset laterality and subsequent cognitive decline (Erro et al., 2013; Katzen, 2006; Poletti et al., 2013), and as it currently stands there appears very little overall consensus. Small sample sizes, the difficulty in controlling for medication effects, time elapsed since disease onset, and methods used for examination of cognitive decline, particularly the reliance upon broad cognitive screening measures as opposed to more specific assessment of individual cognitive domains, have likely contributed to the variable findings and continue to
be factors in current research.

6.1 Aims and Hypotheses

This research proposed to make use of an exploratory approach to further investigate the link between side of onset of motor symptoms and the type and severity of impairment experienced by the participant across a range of cognitive domains. For the current study there were two hypotheses:

- Participants who show unilateral motor symptom onset will display cognitive impairments characteristic of contralateral brain dysfunction.
- Participants who show bilateral motor symptom onset will display a wider range of more severe cognitive impairments when compared to participants with a unilateral motor symptom onset profile.

6.2 Method

6.2.1 Participants

The participants ($n = 88$) for this study were taken from the same cohort examined in Study 1. Additional exclusion criteria included all participants who could not report with certainty their motor symptom presentation at time of disease onset, or who experienced a motor symptom onset profile beyond the scope of the current study (this included one participant who reported her only motor symptom at disease onset to be jaw tremor, and ten participants who were unsure of their initial motor symptoms). Remaining participants ($n = 65$) were divided into three groups based on motor symptom onset laterality (right, RSO; left, LSO; or bilateral, BO). Ethical approval was obtained from the Tasmanian Health and Medical Research Ethics Committee (approval number: H0010104).
6.2.2 Materials

The materials used in Study 2 were the same as those outlined in Study 1.

- The *Hospital Anxiety and Depression Scale* (HADS; Zigmond & Snaith, 1983)
- The *Repeable Battery for the Assessment of Neuropsychological Status* (RBANS; Randolph, 1998)
- The *digit span subtest* from the *Wechsler Adult Intelligence Scale Third Edition* (WAIS III; Wechsler, 1997)
- The *Controlled Oral Word Association Test*
- Part A and Part B of the *Trail Making Test*
- The *Brixton Spatial Anticipation Test* (Burgess & Shallice, 1997)
- The three part *Victoria Stroop Test* (Regard, 1981)
- The two part *Speed of Information Processing* subtest from the *Brain Injury Rehabilitation Trust Memory and Information Processing Battery* (Coughlan, Oddy, & Crawford, 2007)
- The *National Adult Reading Test* (NART; Nelson, 1982)
- A *hand dynamometer* was used to assess grip and muscle strength (Dodrill, 1978)
- The *Finger Tapping Test* (Halstead-Reitan Neuropsychological Test Battery; Reitan & Wolfson, 1993)

6.2.3 Procedure

The procedure used for data collection in Study 2 was the same as outlined in Study 1 as the same participant cohort was used and all data were collected at the same time.
6.2.4 Design and Statistical Analyses

This quasi-experimental design employed one-way ANOVAs with Tukey HSD post hoc measures to detect significant differences between the three groups’ cognitive scores. Cohen’s $d$ analyses were used to calculate effect sizes where appropriate. ANOVA assumptions were checked at the time of data analysis and the homogeneity of error variances was satisfactory, with no large violations of any assumption. Tabachnick and Fidell (2013) say small violations can safely be ignored. The SPSS general linear model used for the analysis also adjusts for differences in sample sizes (Tabachnick & Fidell, 2013). Chi square values were used to examine the frequency with which those in the bilateral motor symptom onset group achieved the lowest scores on each cognitive measure. Chi square values were also used to examine the frequency with which participants in each unilateral motor symptom onset group achieved lower cognitive assessment scores on tests typically claimed to be lateralised to the contralateral hemisphere.

6.3 Results

A one-way ANOVA was used to detect significant between groups differences prior to additional analyses. The BO group size ($n = 5$) presented a challenge for statistical analyses, however, as Table 6.1 indicates, there were no significant between-groups differences for age, years of education, disease duration, or for pre-morbid IQ as estimated by the National Adult Reading Test (NART; Nelson, 1982).
Table 6.1

Descriptive Statistics and One Way ANOVAs for the Three Experimental Groups

<table>
<thead>
<tr>
<th>Factor</th>
<th>RSO (n =33)</th>
<th>LSO (n =27)</th>
<th>BO (n =5)</th>
<th>F</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>67.27 9.38</td>
<td>68.70 10.12</td>
<td>75.00 4.80</td>
<td>1.457</td>
<td>0.241</td>
</tr>
<tr>
<td>Years of education</td>
<td>7.83 8.15</td>
<td>7.09 4.44</td>
<td>13.50 10.33</td>
<td>1.760</td>
<td>0.180</td>
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<tr>
<td>Disease duration</td>
<td>106.49 8.62</td>
<td>106.42a 11.86</td>
<td>103.06 11.86</td>
<td>0.252</td>
<td>0.778</td>
</tr>
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<td>NART FSIQ</td>
<td>6.27 2.99</td>
<td>6.69a 4.03</td>
<td>11.20 5.31</td>
<td>4.025</td>
<td>0.023*</td>
</tr>
<tr>
<td>Anxiety</td>
<td>4.03 2.65</td>
<td>5.42a 3.97</td>
<td>10.40 3.65</td>
<td>8.205</td>
<td>0.001*</td>
</tr>
</tbody>
</table>

* n =26
* p <.05

Note: RSO = right side onset, LSO = left side onset, BO = bilateral onset

Significant differences were found for measures of anxiety and depression, with Tukey HSD post hoc analyses revealing that participants in the BO group were reporting levels of anxiety and depression that were higher than both the RSO and LSO groups, who did not differ significantly from each other and whose group scores lay within the normal range.

Standardised residuals were calculated and used to detect outliers as per Tabachnick and Fidell’s (2013) criteria. Results of this analysis indicated there were no outliers and consequently no participants were excluded on this basis. A copy of the full output for Study 2 can be found in Appendix C2a.

One-way ANOVAs were used to investigate the differences between the three motor symptom onset groups across various cognitive domains. The first investigated differences for the RBANS Total and each of the RBANS Index scores, with results outlined in Table 6.2.
Table 6.2

ANOVAs for the RBANS Total Scaled Score and All RBANS Index Scaled Scores

<table>
<thead>
<tr>
<th>RBANS Scale</th>
<th>RSO (n = 33)</th>
<th>LSO (n = 27)</th>
<th>BO (n = 5)</th>
<th>F</th>
<th>p</th>
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</thead>
<tbody>
<tr>
<td>Total</td>
<td>7.52, 2.88</td>
<td>7.48, 3.02</td>
<td>4.60, 3.58</td>
<td>2.172</td>
<td>0.123</td>
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<td>Imm. Memory</td>
<td>5.88, 3.89</td>
<td>5.81, 3.18</td>
<td>3.40, 3.88</td>
<td>1.069</td>
<td>0.349</td>
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<tr>
<td>Visuospatial/Cons.</td>
<td>10.58, 3.01</td>
<td>9.04, 4.08</td>
<td>7.40, 3.85</td>
<td>2.521</td>
<td>0.089</td>
</tr>
<tr>
<td>Language</td>
<td>9.12, 2.34</td>
<td>9.26, 2.25</td>
<td>7.60, 4.34</td>
<td>0.962</td>
<td>0.388</td>
</tr>
<tr>
<td>Attention</td>
<td>7.58, 2.99</td>
<td>8.00, 3.13</td>
<td>6.40, 5.86</td>
<td>0.520</td>
<td>0.597</td>
</tr>
<tr>
<td>Del. Memory</td>
<td>7.45, 3.80</td>
<td>7.15, 3.61</td>
<td>4.60, 4.93</td>
<td>1.223</td>
<td>0.301</td>
</tr>
</tbody>
</table>

note: RSO = right side onset, LSO = left side onset, BO = bilateral onset

There were no significant between groups differences on either the total RBANS score or any of the individual RBANS indices, however there was a trend towards significance ($p = .089$) for the Visuospatial/Constructional Index, with Tukey HSD pointing towards the difference in mean scores between the RSO group ($M = 10.58$, $SD = 3.01$) and the BO group ($M = 7.40$, $SD = 3.85$). Figure 6.1 depicts the mean scores for all three groups for the Total RBANS scaled score and the five RBANS index scores, with the BO group consistently performing at a level below both the RSO and LSO groups.
Figure 6.1 Mean scaled scores for the right side motor symptom onset (RSO),
left side motor symptom onset (LSO) and bilateral motor symptom onset (BO)
groups for the RBANS Total and all five RBANS indices.

A one-way ANOVA was then used to examine between groups differences
across each individual RBANS subtest. Discrepancy scores for each subtest were
calculated by subtracting each participant’s age corrected expected score from their
actual score, therefore negative values indicate performance below that which would
be expected, while positive values indicate performance at or above that which
would be expected. These discrepancy scores were then used for the analysis, the
results of which have been collated in Table 6.3.
Table 6.3

**ANOVA**s and Relevant Cohen’s d Effect Size for RBANS Subtest Discrepancy Scores

<table>
<thead>
<tr>
<th>RBANS Subtest</th>
<th>RSO (n =33)</th>
<th>LSO (n =27)</th>
<th>BO (n =5)</th>
<th>F</th>
<th>Cohen’s d</th>
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</thead>
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<td></td>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
</tr>
<tr>
<td>List Learning</td>
<td>-6.03</td>
<td>6.85</td>
<td>-6.28</td>
<td>5.01</td>
<td>-10.92</td>
</tr>
<tr>
<td>Story Memory</td>
<td>-4.01</td>
<td>4.73</td>
<td>-3.94</td>
<td>4.21</td>
<td>-7.38</td>
</tr>
<tr>
<td>Figure Copy</td>
<td>0.5</td>
<td>2.09</td>
<td>0.07</td>
<td>2.89</td>
<td>-2.5</td>
</tr>
<tr>
<td>Line Orientation</td>
<td>0.23</td>
<td>2.95</td>
<td>0.07</td>
<td>2.89</td>
<td>-1.26</td>
</tr>
<tr>
<td>Picture Naming</td>
<td>0.06</td>
<td>0.737</td>
<td>0.26</td>
<td>0.41</td>
<td>-0.9</td>
</tr>
<tr>
<td>Semantic Fluency</td>
<td>-0.36</td>
<td>4.53</td>
<td>-0.72</td>
<td>4.94</td>
<td>-3.32</td>
</tr>
<tr>
<td>Digit Span</td>
<td>0.7</td>
<td>3.94</td>
<td>2.54</td>
<td>3.8</td>
<td>0.64</td>
</tr>
<tr>
<td>Coding</td>
<td>-8.02</td>
<td>10.95</td>
<td>-9.05</td>
<td>12.5</td>
<td>-15.24</td>
</tr>
<tr>
<td>List Recall</td>
<td>-1.7</td>
<td>2.57</td>
<td>-1.82</td>
<td>2.11</td>
<td>-2.3</td>
</tr>
<tr>
<td>List Recognition</td>
<td>-1.22</td>
<td>2.3</td>
<td>-1.22</td>
<td>1.86</td>
<td>-1.92</td>
</tr>
<tr>
<td>Story Recall</td>
<td>-1.96</td>
<td>2.92</td>
<td>-1.85</td>
<td>2.26</td>
<td>-3.88</td>
</tr>
<tr>
<td>Figure Recall</td>
<td>-1.08</td>
<td>5.01</td>
<td>-0.83</td>
<td>3.6</td>
<td>-5.28</td>
</tr>
</tbody>
</table>

* p < .05

Note: RSO = right side onset, LSO = left side onset, BO = bilateral onset

As Table 6.3 indicates, there was only one significant result when examining group differences for discrepancy scores on the individual RBANS subtests. Tukey HSD post hoc analysis indicates that the mean Figure Copy discrepancy score for the BO group (M = -2.5, SD = 3.59) was significantly lower than the mean discrepancy score achieved by the RSO group (M = 0.5, SD = 2.09). Figure 6.2 shows the mean discrepancy scores for all RBANS subtests for the three groups (RSO, LSO, & BO) with the BO group achieving lower scores for all variables.
Figure 6.2 Mean discrepancy scores for right side motor onset (RSO), left side motor symptom onset (LSO) and bilateral motor symptom onset (BO) across all RBANS subtests.

A one-way ANOVA was again used to compare between groups differences on a range of cognitive measures outside the RBANS. Results for this analysis can be seen in Table 6.4.
Table 6.4

ANOVA and Relevant Cohen’s d Effect Size for Additional Cognitive Measures

<table>
<thead>
<tr>
<th>Assessment</th>
<th>RSO (n =33)</th>
<th>LSO (n =27)</th>
<th>BO (n =5)</th>
<th>F</th>
<th>Cohen’s d</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean SD</td>
<td>Mean SD</td>
<td>Mean SD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FAS</td>
<td>9.58 3.25</td>
<td>10.08 3.25</td>
<td>7.60 3.65</td>
<td>1.209</td>
<td></td>
</tr>
<tr>
<td>Brixton</td>
<td>3.67 2.29</td>
<td>3.46 2.23</td>
<td>2.60 1.82</td>
<td>0.491</td>
<td></td>
</tr>
<tr>
<td>WAIS Digit Span</td>
<td>9.70 2.70</td>
<td>11.30 2.98</td>
<td>9.60 4.04</td>
<td>2.394</td>
<td></td>
</tr>
<tr>
<td>Trails A</td>
<td>7.937^a 3.42</td>
<td>6.85 3.79</td>
<td>5.20 1.50</td>
<td>1.58</td>
<td></td>
</tr>
<tr>
<td>Trails B</td>
<td>7.839^b 3.07</td>
<td>7.35^c 3.73</td>
<td>7.00^d 4.36</td>
<td>0.192</td>
<td></td>
</tr>
<tr>
<td>Stroop Dots</td>
<td>9.59 3.15</td>
<td>8.21 2.70</td>
<td>6.20 3.03</td>
<td>3.526* 1.100</td>
<td></td>
</tr>
<tr>
<td>Stroop Colours</td>
<td>8.63 3.14</td>
<td>8.08 3.04</td>
<td>6.40 1.95</td>
<td>1.212</td>
<td></td>
</tr>
<tr>
<td>Stroop ColourWord</td>
<td>10.84 3.44</td>
<td>9.63 3.17</td>
<td>8.00 4.24</td>
<td>1.953</td>
<td></td>
</tr>
<tr>
<td>Stroop Interference</td>
<td>11.50 2.70</td>
<td>11.54 3.09</td>
<td>11.40 4.23</td>
<td>0.005</td>
<td></td>
</tr>
</tbody>
</table>

^a n =32, ^b n =31, ^c n =26, ^d n =3

*p <.05

Note: RSO = right side onset, LSO = left side onset, BO = bilateral onset

Results indicated one significant difference for the Stroop Dots condition, with Tukey HSD post hoc analysis revealing the mean standard score for the BO group (M = 6.2, SD = 3.03) was significantly lower than the mean standard score achieved by the RSO group (M = 9.59, SD = 3.15). Figure 6.3 shows the mean scaled scores for all three groups (RSO, LSO & BO) with the BO group mean lower than both the RSO and LSO groups for almost all assessments.
Figure 6.3 Mean scaled scores for the right side motor symptom onset (RSO), left side motor symptom onset (LSO), and bilateral motor symptom onset (BO) groups for additional cognitive measures

Due to the small BO sample size for the one-way ANOVAs, a chi square analysis was conducted to determine whether the mean scores for the participants in the BO group were more often lower than the RSO and LSO groups. Thirty four variables were included in the analysis and to correct for the fact that some observed and expected values fell below five (see Table 6.5), a Yates Correction was also applied.
Table 6.5
Sample Portions and Expected and Observed Lowest Mean Score Values

<table>
<thead>
<tr>
<th>Side of Onset</th>
<th>Proportion of Sample</th>
<th>Expected</th>
<th>Observed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right (n = 33)</td>
<td>0.50</td>
<td>17.00</td>
<td>3.00</td>
</tr>
<tr>
<td>Left (n = 27)</td>
<td>0.42</td>
<td>14.28</td>
<td>3.00</td>
</tr>
<tr>
<td>Bilateral (n = 5)</td>
<td>0.08</td>
<td>2.72</td>
<td>28.00</td>
</tr>
<tr>
<td></td>
<td>(1.0)</td>
<td>(34)</td>
<td>(34)</td>
</tr>
</tbody>
</table>

Results indicated that mean scores for participants in the bilateral (BO) group were significantly more likely to be lower than the means scores for the right (RSO) and left (LSO) sided motor symptom onset groups, \(X^2(2, N = 34) = 244.938, p < .001\).

6.4 Discussion

This study examined the effects of unilateral and bilateral motor symptom presentation at time of disease onset on subsequent cognitive functioning. Although previous research exists examining these relationships, results to date have lacked consistency.

6.4.1 Right versus Left Motor Symptom Onset

While the current study hypothesised that participants in the two unilateral motor symptom onset groups (RSO & LSO) would display cognitive impairments characteristic of contralateral brain dysfunction, no significant differences were found between the two groups for any of the assessment measures examined. This result is partly in keeping with similar research completed by Cooper et al. (2009) who, when examining current motor symptom presentation, found no association between left side motor impairment and cognitive domains believed to be dominated...
by the contralateral brain regions, as well as no association between left or right side motor impairment and executive functioning. However Cooper et al. (2009) did find a significant association between right side motor impairment and verbal memory, verbal fluency and visuospatial skills. More recently, Erro et al. (2013) and Poletti et al. (2013), both found no significant effects when examining the impact of motor symptom laterality on various measures of cognitive functioning in newly diagnosed and as yet untreated people with PD. Dewey et al. (2012), retrospectively examining side of motor symptom at disease onset, also found no effect of laterality on cognitive functioning. In summary, evidence to date would suggest that there is no lateralisation of cognitive functioning at a subcortical level to mirror that which has been established at a cortical level.

6.4.2 Bilateral versus Unilateral Motor Symptom Onset

The current study hypothesised that participants with bilateral motor symptom onset would display a wider range of cognitive impairments when compared to participants with unilateral motor symptom onset. It is likely that the very few significant ANOVA results found for the effect of bilateral motor symptom onset are in part due to the size of the sample (BO, n = 5). Only two measures, Stroop Dots and the Figure Copy subtest from the RBANS, reached significance (p < .05), with post hoc measures indicating that the mean scores for those in the BO group were significantly lower than the mean scores achieved by those in the RSO group for both measures.

In an effort to further investigate the differences between the groups, chi square analysis was employed to examine the frequency with which each of the three groups performed poorest on the individual assessment measures. With some
expected and observed values falling below five, a Yates Correction was applied to the data. The result from this analysis was highly significant \( (p < .001) \) with the BO group performing poorest on 28 of the 34 individual measures included in this study.

The suggestion that people with PD with a bilateral motor symptom onset are more at risk of cognitive decline than those with a unilateral motor symptom onset is a result supported by Viitanen et al. (1994) who, when retrospectively examining initial motor symptom presentation, found bilateral onset to be predictive of a more severe cognitive decline profile as measured by the MMSE.

It is important to note that participants in the current study were divided into the three experimental groups (RSO, LSO, & BO) based on the presentation of their motor symptoms at time of disease onset. While there were some participants in both the RSO and LSO groups who were currently experiencing a bilateral motor symptom presentation profile, they were not included in the BO group due to the fact that their symptoms had begun as unequivocally unilateral and were instead allocated to a group on the basis on their initial unilateral symptom onset. This may suggest that people with PD experiencing bilateral motor symptoms at onset are not only at greater risk of cognitive decline when compared to people with unilateral onset, but also when compared to people who begin with unilateral onset but eventually develop bilateral motor symptoms as the disease progresses.

6.4.3 The Effects of Mood on Cognitive Performance in PD

Initial one way ANOVAs in the current study indicated a significant between groups difference for both anxiety \( (p = 0.023) \) and depression \( (p = 0.001) \) as measured by the HADS. Post hoc analyses clearly indicated that participants in the BO group were reporting significantly higher levels of anxiety and depression.
symptoms than both the RSO and LSO groups, who did not differ significantly from each other.

This study included the HADS in the assessment battery as a tool to measure current mood levels. Despite the fact that mood was not one of the experimental variables identified for this study prior to analysis, the detrimental effects of anxiety and depression symptoms on cognition are well documented and thus, require interpreting in this context. Using a cut-off score of 8 for both the anxiety and depression components of the HADS as suggested by Bjelland et al. (2002), three of the five participants in the BO group were classified as experiencing symptoms of both anxiety and depression, while one was classified as experiencing anxiety symptoms only and the other as depression symptoms only. Mean anxiety and depression ratings for the RSO group (HADS-A, $M = 6.27$; HADS-D, $M = 4.03$) and the LSO group (HADS-A, $M = 6.69$; HADS-D, $M = 5.42$) both fell below the recommended clinical cut-off and within the normal range.

Firstly, it is important to note that the sample size of the BO group was quite small ($n = 5$), and this may have had an impact on the findings. However, post hoc correlations were also conducted (see Appendix C2b for full output) to more closely examine this result. While positive correlations were found between anxiety and/or depression and several of the cognitive measures, some of these, for example the Stroop Dots condition and Trails A, involve a timed component and rely heavily on motor functioning, factors known to be significantly affected by the confounding presence of both Parkinson’s disease and mood disorders. There were no correlations of any meaningful size between anxiety and/or depression and the cognitive measures less reliant on motor functioning, such as the Stroop Interference condition, the Brixton Spatial Anticipation Test, Digit Span, and the adjusted
information processing score for the BMIPB where motor speed is accounted for. In fact, of the 32 correlations in the analysis, 20 fell below $r = 0.2$ and of the remaining 12, 7 involved a timed component, making it difficult to determine whether the performance was due to the presence of a mood disorder or the result of the impaired motor functioning associated with PD.

There is some research beginning to emerge suggesting that side of onset may play a role in the presence depression and apathy and, in turn, on subsequent cognitive functioning (Foster, Yung, Drago, Crucian, & Heilman, 2013; Harris, McNamara, & Durso, 2013). However, neither of these studies examined the impact of bilateral disease onset and additional research is required before definitive conclusions can be drawn. Study 3 of this research takes a closer look at the effects of motor symptoms on the measurement of anxiety and depression in PD using the HADS.

6.4.4 Limitations of the Current Study and Suggestions for Future Research

It is acknowledged that a potential limitation of the current study is group size, particularly for participants with bilateral motor symptom onset. As with Study 1, the large number of variables included in the current study has had an impact on the statistical power of the analyses. Again, the approach to this study was exploratory in nature, with little to no previous research having been conducted on the impact of side of motor symptoms at disease onset and the majority of the cognitive domains included. This study should be used as a platform for targeting more specific cognitive domain research in the future.

In addition to this, the current research only accounted for side of motor symptom at onset and did not also account for type of motor symptom at onset.
(tremor, bradykinesia/rigidity etc). Recent research (for example, Katzen et al., 2006) has suggested that the type of motor symptom at onset is an important factor when examining the relationship between motor symptoms and subsequent cognitive decline in PD and it is recommended that any future research in this area attempt to address this.

It is recommended that future research attempt to include functional imaging data where possible. While imaging was beyond the scope of the current study due to financial limitations, it is possible that the addition of imaging could have provided a clearer illustration of any potential subcortical differences between the three groups. It is also recommended that longitudinal research be undertaken that examines the effects of side of onset at the time of diagnosis and follows this through for a number of years. Typically, data collected in this area to date has been from a single time point, with factors such as time since diagnosis potentially confounding results. A longitudinal design where all participants are tracked similarly would be beneficial to understanding disease progression and its relationship to symptoms presenting at diagnosis.
CHAPTER SEVEN

STUDY 3: Exploratory investigation of the effects of motor symptoms on the assessment of mood in Parkinson’s disease

As reviewed in Chapter Three, non-motor symptoms of anxiety and depression are common in PD populations, with reported frequencies of between 40 and 50% for both (Dobkin et al., 2012; Leetjens et al., 2011; Mondolo et al., 2006; Schrag et al., 2007).

Due to overlap with the motor symptoms associated with PD and the complications inherent in assessing mood in individuals experiencing cognitive decline or dementia, accurate assessment of the presence of anxiety and depression in PD populations has proved difficult.

The Hospital Anxiety and Depression Scale (HADS; Zigmond & Snaith, 1983) is a fourteen item, self-report scale that requires the patient to consider the past one week when providing answers. Clinical cut-offs both for symptoms of anxiety (HADS A scores) and depression (HADS D scores) have been established. Traditionally, the HADS has been viewed as a particularly useful tool in detecting symptoms of anxiety and depression in PD populations due to the deliberate way in which the creators attempted to minimise the inclusion of any questions that might also represent somatic symptoms characteristic of injury or other physical disorders (Bjelland et al., 2002). Marinus, Leentjens, Visser, Stiggelbou, & van Hilten (2002), in examining the use of the HADS in PD populations, concluded that it is a psychometrically valid measure for detecting symptoms of anxiety and depression.
In contrast to this however, other research has called into question the validity of the HADS as an accurate tool for measuring symptoms of anxiety in particular but also symptoms of depression in a PD population, with some researchers concluding that it should be used with caution (Leentjens et al., 2008).

Despite Zigmond and Snaith’s intent to limit items in the HADS that may also reflect somatic complaints or physical injuries, several studies have clearly indicated that this is still a significant issue inherent in the scale when used with people having experienced traumatic brain injuries (Skilbeck, Holm, Slatyer, Thomas, & Bell, 2011), acquired amputations (Desmond & MacLachlan, 2005), acquired brain injuries (Dawkins, Cloherty, Gracey, & Evans, 2006), clinical depression (Friedman, Samuelian, Lancrenon, Even, & Chiarelli, 2001) and coronary heart disease (Martin, Lewin, & Thompson, 2003). As PD is an illness that involves a large number of varied motor symptoms, these findings are particularly relevant to the use of the HADS in this clinical population. There are still several items included in this self-report questionnaire that may well be influenced by the PD patient’s motor symptom presentation. For example:

“I feel tense or ‘wound up’” (HADS A)

“I feel as if I am slowed down.” (HADS D)

“I feel restless, as if I have to be on the move.” (HADS A)

A large-scale review conducted by a Movement Disorder Society taskforce (Leentjens et al., 2008) concluded that the clinimetric properties of scales (including the HADS) commonly used to assess anxiety in particular in PD populations have not been adequately evaluated. More recent researchers have also supported this
claim (Martinez-Martin et al., 2013). In addition to this, Leentjens et al (2011) found that a three-factor solution for the HADS in a PD population accounted for 62% of the variance (Eigenvalue > 1), while the more traditional two-factor solution accounted for 54% of the variance. These researchers also found that when analysing the traditional two-factor model, some of the HADS A items loaded onto the HADS D factor and vice versa (Leentjens et al., 2011).

Despite this, little exists in current literature that adequately establishes via confirmatory factor analysis a three-factor model for administering and interpreting the HADS in a PD population.

Exploratory factor analysis \( (n = 186) \) followed by confirmatory factor analysis \( (n = 185) \) of the fourteen HADS items using people with traumatic brain injury (TBI) has found that a three-factor model may provide a more clinically relevant fit for the scale in a TBI population (Holm, 2013; Skilbeck et al., 2011). As suggested by Leentjens et al (2011), a three-factor model may also be more clinically relevant for a PD population, and the statistically sound development of a three-factor model provides the opportunity to further explore this; particularly, does motor symptom presentation in PD differentially affect the three factors?

In addition to this, little is known about the impact of side of initial motor symptom onset and the subsequent experience of symptoms of anxiety and depression as measured by the HADS. Results from Study 2 of this research suggest that those with bilateral motor symptoms at disease onset subsequently report more symptoms of anxiety and depression than those with unilateral onset; however more research is required before definitive conclusions can be drawn.
7.1 Aim

This third study was exploratory in nature and aimed to examine the effects of current level motor functioning and side of initial motor symptom onset on the original two-factor model of the HADS, and a three-factor model that included an additional psychomotor scale.

7.2 Method

7.2.1 Participants

The participants \((n = 88)\) for this study were taken from the same cohort examined in Study 1 and Study 2. Exclusion criteria remained the same. Additional exclusion criteria included any participant who did not complete all motor functioning subtests of the overall assessment battery. For the motor functioning component of this study, and on the basis of a composite motor functioning discrepancy score, obtained by adding age and gender corrected discrepancy scores together for the three key motor functioning measures (motor speed, grip strength as measured by the hand dynamometer, and manual dexterity as measured by the Finger Tapping Test), remaining participants \((n = 62)\) were divided into two groups using a median split; higher functioning (discrepancy scores between \(-26 & 38\)) and lower functioning (discrepancy scores between \(-27 & -61\)). For the side of onset component, eligible participants were divided into three groups based on their initial motor symptom presentation (right sided, left sided, or bilateral).

Ethical approval was obtained from the Tasmanian Health and Medical Research Ethics Committee (approval number: H0010104).
7.2.2 Materials

- The Hospital Anxiety and Depression Scale (Zigmond & Snaith, 1983)
- Hand dynamometer (Dodrill, 1978)
- The Finger Tapping Test (Halstead-Reitan Neuropsychological Test Battery; Reitan & Wolfson, 1993)
- The two part Speed of Information Processing subtest from the Brain Injury Rehabilitation Trust Memory and Information Processing Battery (Coughlan, Oddy, & Crawford, 2007)

7.2.3 Procedure

The procedure used for data collection in this study was the same as outlined in Study 1 as the same participant cohort was used and all data was collected at the same time.

The HADS was scored using two different methods. Firstly, the original two-factor HADS A and HADS D scoring was completed as per the instructions established by Zigmond and Snaith (1983). In addition to this, each participant’s results were recorded according to a three-factor model of the HADS, established by Skilbeck et al (2011), that also includes a third psychomotor factor (see Table 7.1).
Table 7.1

*Three-factor Model of the HADS in a TBI Population as Identified Using CFA (Skilbeck et al., 2011)*

<table>
<thead>
<tr>
<th>HADS Item</th>
<th>Anxiety</th>
<th>Psychomotor</th>
<th>Depression</th>
</tr>
</thead>
<tbody>
<tr>
<td>HADS A</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I feel tense or 'wound up'</td>
<td>0.55</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I get a sort of frightened feeling as if something awful is about to happen</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Worrying thoughts go through my mind</td>
<td>0.76</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I can sit at ease and feel relaxed</td>
<td>0.78</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I get a sort of frightened feeling like 'butterflies' in the stomach</td>
<td></td>
<td></td>
<td>0.78</td>
</tr>
<tr>
<td>I feel restless as if I have to be on the move</td>
<td>0.60</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I get sudden feelings of panic</td>
<td>0.88</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HADS D</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I still enjoy the things I used to enjoy</td>
<td>0.69</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I can laugh and see the funny side of things</td>
<td></td>
<td>0.45</td>
<td></td>
</tr>
<tr>
<td>I feel cheerful</td>
<td>0.68</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I feel as if I am slowed down</td>
<td>0.42</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I have lost interest in my appearance</td>
<td></td>
<td></td>
<td>0.59</td>
</tr>
<tr>
<td>I look forward with enjoyment to things</td>
<td></td>
<td></td>
<td>0.87</td>
</tr>
<tr>
<td>I can enjoy a good book or radio or television programme</td>
<td></td>
<td></td>
<td>0.64</td>
</tr>
</tbody>
</table>

7.2.4 *Design and Statistical Analyses*

This quasi-experimental design used independent samples t-tests and One-way ANOVAs and Tukey’s HSD post hoc tests to analyse the data. Cohen’s $d$ calculations were used to determine effect sizes where appropriate.
7.2 Results

7.2.1 Current Motor Functioning

An independent samples t-test was carried out to detect any significant between groups differences on demographic factors including age, years of education, premorbid intelligence as estimated by the NART, and disease duration. As displayed in Table 7.2, there were no significant differences between the two experimental groups on any of these factors.

Table 7.2

<table>
<thead>
<tr>
<th></th>
<th>Lower (n =25, males=13)</th>
<th>Higher (n =25, males=9)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
</tr>
<tr>
<td>Age</td>
<td>70.80</td>
<td>9.241</td>
</tr>
<tr>
<td>Years of education</td>
<td>10.60</td>
<td>2.327</td>
</tr>
<tr>
<td>NART FSIQ</td>
<td>106.70</td>
<td>10.073</td>
</tr>
<tr>
<td>Years since PD dx</td>
<td>8.78</td>
<td>7.149</td>
</tr>
</tbody>
</table>

Note: lower = lower motor functioning, higher = higher motor functioning

Independent samples t-tests were also used to analyse the mean score differences between the two experimental groups on both the two-factor and the three-factor HADS. As illustrated in Table 7.3, there were no significant differences between the two groups on symptoms of anxiety or depression as traditionally determined by the original two-factor interpretation of the HADS, indicating that anxiety and depression symptom reporting did not differ on the basis of current motor functioning levels. The three factor version of the HADS (Skilbeck et al., 2011), again indicated no significant differences between the two motor functioning
groups on self-reported symptoms of anxiety and depression, however there was a significant between groups difference on mean scores for the psychomotor factor. These results are also summarised in Table 7.3.

Table 7.3

*Independent Samples T-test Results for Both Motor Functioning Groups on the Two and Three Factor HADS*

<table>
<thead>
<tr>
<th></th>
<th>Lower (n =25, males=13)</th>
<th>Higher (n =25, males=9)</th>
<th>t</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Two Factor</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anxiety</td>
<td>8.08 4.071</td>
<td>6.04 3.446</td>
<td>1.912</td>
<td>0.062</td>
</tr>
<tr>
<td>Depression</td>
<td>5.92 4.377</td>
<td>4.76 3.382</td>
<td>1.048</td>
<td>0.300</td>
</tr>
<tr>
<td><strong>Three Factor</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anxiety</td>
<td>6.59 2.400</td>
<td>5.66 1.781</td>
<td>1.512</td>
<td>0.137</td>
</tr>
<tr>
<td>Depression</td>
<td>4.71 1.960</td>
<td>4.39 1.562</td>
<td>0.629</td>
<td>0.532</td>
</tr>
<tr>
<td>Psychomotor</td>
<td>7.97 2.568</td>
<td>6.64 1.411</td>
<td>0.419</td>
<td>0.031*</td>
</tr>
</tbody>
</table>

*note: lower = lower motor functioning, higher = higher motor functioning*

An additional Cohen’s $d$ calculation revealed a moderate effect size for the significant psychomotor factor, $d=0.64$. Full output can be viewed in Appendix C3a.

### 7.2.2 Side of Motor Symptom Onset

A one-way ANOVA was carried out to detect any significant between groups differences on demographic factors such as age, years of education, premorbid intelligence as estimated by the NART, and disease duration. As displayed in Table 7.4, there were no significant differences between the two experimental groups on any of these factors.
Table 7.4

Descriptive Statistics and ANOVA Results for Demographic Variables

<table>
<thead>
<tr>
<th>Factor</th>
<th>RSO (n=33)</th>
<th>LSO (n=27)</th>
<th>BO (n=5)</th>
<th>F</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>67.27</td>
<td>68.70</td>
<td>75.00</td>
<td>1.457</td>
<td>0.241</td>
</tr>
<tr>
<td>Years of education</td>
<td>10.70</td>
<td>11.04</td>
<td>10.40</td>
<td>0.175</td>
<td>0.840</td>
</tr>
<tr>
<td>Disease duration</td>
<td>7.83</td>
<td>7.09</td>
<td>13.50</td>
<td>1.760</td>
<td>0.180</td>
</tr>
<tr>
<td>NART FSIQ</td>
<td>106.49</td>
<td>106.42</td>
<td>103.06</td>
<td>0.252</td>
<td>0.778</td>
</tr>
</tbody>
</table>

* note: RSO = right side onset, LSO = left side onset, BO = bilateral onset

An additional one-way ANOVA was used to examine the differences between the means for the three experimental groups on both the two-factor and three-factor HADS. As illustrated in Table 7.5, significant differences between the groups (RSO, LSO & BO) were found for anxiety and depression symptoms for both the two-factor and the three-factor HADS, but not for the psychomotor symptoms as identified by the three-factor HADS.

Table 7.5

One-way ANOVA Results for the Two-factor and Three-factor HADS

<table>
<thead>
<tr>
<th>HADS</th>
<th>RSO (n=33)</th>
<th>LSO (n=26)</th>
<th>BO (n=5)</th>
<th>F</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Two-Factor</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anxiety</td>
<td>6.27</td>
<td>6.69</td>
<td>11.20</td>
<td>4.025</td>
<td>0.023*</td>
</tr>
<tr>
<td>Depression</td>
<td>4.03</td>
<td>5.42</td>
<td>10.40</td>
<td>8.205</td>
<td>0.001**</td>
</tr>
<tr>
<td>Three-Factor</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anxiety</td>
<td>5.65</td>
<td>5.86</td>
<td>8.76</td>
<td>5.507</td>
<td>0.006**</td>
</tr>
<tr>
<td>Depression</td>
<td>4.02</td>
<td>4.57</td>
<td>6.19</td>
<td>4.250</td>
<td>0.019*</td>
</tr>
<tr>
<td>Psychomotor</td>
<td>7.11</td>
<td>7.07</td>
<td>8.97</td>
<td>1.993</td>
<td>0.145</td>
</tr>
</tbody>
</table>

* n=24, b n=25,
* p <.05, ** p <.01

note: RSO = right side onset, LSO = left side onset, BO = bilateral onset

Tukey’s HSD post hoc analyses indicated that for the two-factor HADS, participants in the BO group reported significantly more symptoms of anxiety and depression than participants in both unilateral onset groups (RSO & LSO), while the
RSO and LSO groups did not differ significantly from each other. Likewise, post hoc analyses indicated that for the three-factor HADS, participants in the BO group reported significantly more symptoms of anxiety and depression than participants in both unilateral onset groups and, again, those unilateral onset groups did not differ significantly from each other. Full output can be viewed in Appendix C3b.

For the two-factor HADS anxiety results, the Cohen’s $d$ effect size between the means for the RSO and BO groups was very large, $d = 1.14$. There was a large effect size for the difference between the means for the LSO and BO groups, $d = .96$. For the two-factor HADS depression results, the Cohen’s $d$ effect size between the means for the RSO and BO groups was very large, $d = 2.0$. Likewise, there was a very large effect size for difference between the means for the LSO and BO groups, $d = 1.31$.

For the three-factor HADS anxiety results, the Cohen’s $d$ effect size between the means for the RSO and BO groups was very large, $d = 1.36$, as was the effect size between the LSO and BO groups, $d = 1.25$. For the three-factor HADS depression results, the Cohen’s $d$ effect size between the means for the RSO and BO groups was very large, $d = 1.31$, while there was a moderate effect size between the LSO and BO groups, $d = .85$.

### 7.3 Discussion

The current study aimed to examine the effects of current level motor functioning and initial side of motor symptom onset in a PD population on the original two-factor model of the HADS, and a three-factor model that also included an additional psychomotor scale. There were no explicit hypotheses proposed as the study was exploratory in nature.
Initial analyses showed no significant between groups differences on demographic factors such as age, years of education, disease duration, or premorbid functioning as estimated by the NART.

7.3.1 Effects of Motor Functioning on the Two and Three-Factor HADS

As the results for this study indicate, there were no significant differences detected between the two motor functioning groups when analysing responses according to the two-factor approach to the HADS, though there was a trend towards significance for the anxiety factor ($p = .062$). However, when examining responses according to Skilbeck et al’s (2011) three-factor model, a significant difference was found for the psychomotor factor, with participants in the lower motor functioning group exhibiting significantly higher psychomotor scores than their higher motor functioning group counterparts. Post hoc analyses indicated that this significant difference had a moderate ($d = 0.64$) effect size.

This result is in keeping with previous research suggesting the HADS be interpreted with caution in PD populations (Leentjens et al., 2008; Martinez-Martin et al., 2013).

7.3.2 Effects of Side of Motor Symptom Onset on the Two and Three-factor HADS

This study also examined the impact of side of motor symptoms at disease onset on subsequent reporting of anxiety and depression symptoms using both the two and three-factor HADS. As with the motor functioning component of this study, in the three-factor HADS items loading on the third, psychomotor, factor were removed from the anxiety and depression factors. As the results clearly indicate, participants with bilateral motor symptoms at onset reported significantly greater
levels of both anxiety and depression on both versions of the HADS than either of the unilateral (RSO or BSO) groups. This suggests that bilateral motor symptom onset may be predictive of increased risk for anxiety and depression symptoms. There were no significant differences between the RSO and LSO groups across either the two-factor or the three-factor HADS, suggesting that when it comes to unilateral motor symptom onset, the initial side, right or left, is not a relevant factor in the subsequent development of symptoms of anxiety and/or depression.

It is interesting to note that, using cut-offs well established for the two-factor HADS, the BO group reported clinically significant levels of both anxiety and depression, while participants in the unilateral onset groups scored in the normal ranges. As yet, there are no established clinical cut-offs for the three-factor HADS that would be appropriate for providing a comparison in this instance.

There were no significant psychomotor differences between the three groups on the three-factor HADS. This result lends further support to the suggestion that certain items in the current HADS questionnaire do not examine the presence of anxiety and depression in people with PD in the manner that was originally intended and, instead, may examine the presence of psychomotor symptoms.

7.3.3 Implications for Clinical Use of the HADS in PD

At this stage, it is difficult to draw definitive conclusions about the use of the HADS in a PD population; however it is clear that motor symptom presentation plays a key role in item responding. It is possible that traditional ‘anxiety factor’ items (for example: ‘I can sit at ease and feel relaxed’) that load more heavily onto a third factor are not providing useful information regarding levels of anxiety in PD populations and are perhaps reflective of the patient’s current degree of motor
functioning as opposed to their mood. Likewise, this may also be the case for some traditional ‘depression factor’ items, such as, ‘I can enjoy a good book or radio or television programme.’ Common sense would tell us that these items are likely to be affected by more severe motor symptoms which have the potential, at times, to make such activities physically impossible for the patient.

However, it is also important to consider that if a patient’s more severe motor symptom presentation physically prevents them from ‘sitting at ease’ and ‘feeling relaxed’, this does not preclude them from also experiencing symptoms of anxiety. The issue here is that there is an assumption inherent in the scale that, for example, ‘I can sit at ease and feel relaxed’ only measures anxiety, when that may not be the case in a PD population. The patient may endorse a HADS A item due to motor factors rather than mood factors. Therefore, results from the traditional HADS A and HADS D scales can be misleading and should be used with caution.

In addition to this, and as results from this study have indicated, a three-factor model of the HADS may be capable of distinguishing between higher and lower motor functioning groups of people with PD, which is a potentially useful finding in its own right and is supported by findings in other clinical populations (Desmond & MacLachlan, 2005; Martin, 2005).

7.4 Limitations of the Current Study and Suggestions for Future Research

At the time of this study, a rigorous confirmatory factor analysis of the HADS for use in a PD population could not be sourced; consequently the three-factor TBI model was used. It is acknowledged that use of a solution for the HADS based specifically on a PD population would have been beneficial, and any future research
investigating the validity of the HADS for people with PD should seek to include this.

It is recommended that a tool designed specifically for assessing the significance of anxiety and depression symptoms in PD be developed. Reliance on tools developed for populations that do not experience the same degree of symptom overlap as is seen in PD is problematic, and may be significantly impacting accurate diagnosis and appropriate treatment of these disorders.

Finally, it is acknowledged that the sample size for the BO group was very small ($n = 5$) and additional research with a larger group of people with bilateral onset would be beneficial.
CHAPTER 8

General Discussion

Parkinson’s disease is the second most common neurodegenerative disorder after Alzheimer’s disease with a reported prevalence rate of approximately 1% in people aged 60 years and over. This prevalence rate increases with advancing age (Fritsch et al., 2012). While traditionally believed to be a disorder producing only motor symptoms, this understanding has since been proven unequivocally false, with the disease also involving a large and varied number of non-motor symptoms that can have a significant impact on quality of life, ability to carry out activities of daily living, and carer burden.

While the majority of motor symptoms involved in PD are generally well understood, with a number of effective treatment options having been developed over recent years, non-motor symptoms still provide an area of significant debate. This is particularly the case with regard to the pathophysiology of mild cognitive decline and Parkinson’s disease dementia, the accurate assessment of mood symptoms, and the exact nature of the complicated relationship that exists between motor and non-motor symptom presentation.

The focus of the current thesis was to add to the growing body of literature that has examined the impact of motor symptom severity and side of motor symptom onset on subsequent cognitive decline, and also to investigate the effects of motor functioning on the assessment of anxiety and depression symptoms in PD.
8.1 Overview of the Findings

Study 1 examined 50 people diagnosed with idiopathic PD. Results supported the initial hypothesis that poorer current motor functioning would be associated with significantly more severe cognitive decline. This was particularly true for tasks involving executive functioning, and visuospatial skills, which is in keeping with the current understanding of the areas of cognitive functioning most affected by the development of PD. In comparison to this, Study 2, using 65 people diagnosed with idiopathic PD, disregarded motor symptom severity and instead focussed on the side of the participant’s motor symptom onset in an attempt to establish further evidence for a link between side of onset and type of cognitive decline. It was hypothesised that participants who experienced right sided motor symptom onset would perform more poorly on tasks related to left hemisphere cognitive functioning, while those who experienced left sided motor symptom onset would perform more poorly on tasks related to right hemisphere cognitive functioning as understood by theories of hemispheric specialisation. Little is known about the potential laterality of subcortical regions and it was thought that a pattern similar to that which exists at a cortical level may be present. Results, however, did not support this hypothesis, with no discernible pattern emerging between side of motor symptom onset and type of cognitive decline.

In addition to this, Study 2 also examined the impact of bilateral motor symptom onset on cognitive decline, with the hypothesis suggesting that bilateral onset would result in poorer cognitive performance than unilateral onset. Despite a very small sample size for the bilateral onset group, underlining the rarity with which this initial symptom presentation occurs in the general PD population, results were still highly significant. Participants who indicated they’d experienced bilateral motor
symptom onset performed more poorly that those with unilateral motor symptom onset on 82% of the cognitive functioning measures included in the assessment battery. This is especially pertinent given the fact there were participants in the unilateral onset groups (right and left) who were currently experiencing bilateral motor symptoms but who had only unilateral symptoms at disease onset. This result underlines the fact that it is likely the presentation of motor symptoms at disease onset will provide clinicians the richest source of information for predicting cognitive decline as disease progresses.

An additional component to Study 1 involved completing a series of stepwise regression analyses in order to determine the capacity of various motor functioning measures to predict cognitive decline. Motor functioning measures included in these analyses were motor speed as measured by the BMIPB, dominant and non-dominant Finger Tapping Test results, and dominant and non-dominant hand dynamometer results. All of these scores were age and gender corrected prior to the analysis. In step two of the regression, additional demographic factors were included such as age, sex, disease duration, premorbid FSIQ estimate as measured by the NART, and years of education. This component of the study was exploratory in nature, and involved no specific hypotheses.

Results indicated that motor speed scores accounted for a significant portion of the variance on a considerable number of cognitive tasks. This was even true for cognitive tasks that did not involve a timed component and relied very little or not at all on motor functioning, such as the Brixton Spatial Anticipation Test. This is consistent with the suggestion of an executive deficit component to PD. In contrast to motor speed, the other motor functioning measures rarely featured in the
regression models. Of the demographic variables examined, sex, years of education, and premorbid FSIQ were the most prominent.

Study 3, involving 62 people diagnosed with idiopathic PD, examined the effects of motor functioning and side of motor symptom onset on the self-report of symptoms of anxiety and depression using both the original two-factor version of the HADS and a more recently devised three-factor version from TBI research. As reviewed in Chapter Three, the HADS was designed specifically to eliminate the effects of somatic complaints and physical injuries and illnesses on symptom reporting, as there can be significant overlap in some instances, particularly with symptoms such as fatigue and dizziness (Bjelland et al., 2002; Zigmond & Snaith, 1983). Because of this, it has generally been viewed as an appropriate option for use in non-psychiatric clinical populations, including PD (Marinus et al., 2002). However, even just examining the wording of some of the included items will raise flags about their validity in a PD population, for example, “I can sit at ease and feel relaxed.” More recently, research has been calling into question the use of this measure in its traditional two-factor (HADS A & HADS D) form in a PD population (Leentjens et al., 2011; Leentjens et al., 2008), and results from this third study support this view.

When interpreting the HADS in its traditional two-factor manner, there were no significant differences found between the lower motor functioning group and the higher motor functioning group, with both groups reporting similar levels of both anxiety and depression symptoms. However, when interpreting the results using Skilbeck et al.’s (2011) three-factor model, devised using both exploratory factor analysis (EFA) and confirmatory factor analysis (CFA) within a TBI population, a significant difference was found between the lower motor functioning group and the
higher motor functioning group on the additional psychomotor factor. Participants with lower motor functioning self-reported significantly more psychomotor symptoms than participants with higher motor functioning.

This study also examined the impact of side of motor symptom onset on subsequent reporting of anxiety and depression symptoms. Results clearly indicated participants with bilateral motor symptoms at onset report significantly greater levels of both anxiety and depression on both versions of the HADS than either of the unilateral (RSO or BSO) groups. This suggests that bilateral motor symptom onset may be predictive of increased risk for subsequent symptoms of anxiety and depression. There were no significant differences between the three groups on the psychomotor scale when analysing results using the three-factor HADS. This further supports the claim that certain items in the current HADS questionnaire do not examine the presence of anxiety and depression in people with PD in the manner that was originally intended and, instead, may examine the presence of psychomotor symptoms which do not differ between groups according to laterality of initial motor symptom onset.

As outlined in the conclusion of Study 3, at this stage it is difficult to draw definitive conclusions regarding the significance of this finding, and additional research using a CFA devised model of the HADS specific to PD is recommended.

8.2 Clinical Implications

As PD is a degenerative disease that progresses over time and can reach a point of frank dementia, an early understanding of a patient’s prognosis is extremely useful, not only for the clinician, but also for the patient and the patient’s family members/carers. This sort of information can be used to help encourage people with
PD to adhere to treatment regimes, to prepare them for the likely challenges that lay ahead in a manner this is not detrimental to their emotional well-being, to allow them to make informed decisions regarding riskier surgical treatment options such as DBS, and to ensure they can broach the medico-legal complications of their diagnosis at a time when they’re still fully capable of doing so.

In addition to this, symptoms of PD can include pain and fatigue, both of which can make validly completing lengthy and complicated neuropsychological assessments difficult. It is important that increasingly busy clinicians can easily identify assessment measures known to be appropriate for people with PD as this can reduce the need for additional assessments and ensures the most useful information is gathered in the most efficient manner.

This research has identified several aspects of background information that can be used to assist development of a wider prognostic picture for the patient. This includes obvious factors such as sex and age, but also years of education, premorbid FSIQ estimates, and whether the initial motor symptom onset was bilateral or unilateral.

The current study also added to research highlighting motor symptom severity and the presence of bilateral motor symptoms at disease onset as a valuable tool for predicting subsequent cognitive decline, particularly for executive functioning and visuospatial tasks (Arnaldi et al., 2012).

The current study also added to the growing body of research in the PD arena that questions the clinical utility of the HADS as an accurate tool for measuring symptoms of anxiety and depression (Leentjens et al., 2011; Leentjens et al., 2008; Martinez-Martin et al., 2013). While it is acknowledged that additional research is required before definitive conclusions can be reached regarding the use of the HADS
in PD, it is possible to suggest that the impact of motor functioning on endorsement of individual items means results obtained using the HADS should be interpreted cautiously.

8.3 Limitations of the Current Research

Limitations specific to each of the individual studies can be found in the relevant discussion sections, however the fact that medication regimes could not be controlled for was common to all three. As reviewed in Chapter One, there are a number of medications approved for the management and treatment of PD symptoms. These medications vary in a number of ways, including biochemically, and with regard to the effects they have on symptoms. Even the same medication can vary in effectiveness and side-effect profile between people with PD. The use of mood stabilisers, antipsychotics, and/or anxiolytics is also common in people with PD in order to treat non-motor symptoms such as depression, anxiety, and hallucinations. People with PD involved in the current research each had a medication regime designed specifically to manage their unique symptom profile, and each differed quite considerably to the medication regimes of other people. While many of the medications were common among the participants, dosage amounts, frequencies, and times varied, and it was beyond the scope of the current research to control for this.

In addition to treatments specific to PD, many people had also been prescribed medications for co-morbid ailments such as high blood pressure, high cholesterol, diabetes, and pain. It is difficult to determine what, if any, effects these medications had on the results obtained.
Controlling for the effects of anti-parkinsonian medications is a methodological barrier inherent in almost all PD research and makes it very difficult to isolate the effects of the disease from the effects of the treatments. Conducting research on drug-naïve de novo people with PD is a potential solution to this issue (Planetta, McFarland, Okun, & Vaillancourt, 2013; van der Vegt et al., 2013), and while it is acknowledged that controlling for medication effects in this population of participants would be very difficult, research that attempts to do just that would be beneficial.

8.4 Future Directions

Recommendations for future research specific to the three studies involved in this thesis have been detailed in the relevant discussion sections.

With regard to Parkinson’s disease research in general, and in line with the recommendation for future research made by the National Institute of Health (2013) that suggests an increase in the investigation of non-motor symptoms in PD due to their debilitating nature and severe impact on quality of life, it is suggested that future research continue attempts to unravel the pathophysiology of not only cognitive decline in PD, but also anxiety and depression.

Future research should also seek to make use of evolving magnetic resonance imaging (MRI) techniques such as diffusion tensor imaging (DTI; Cochrane & Ebmeier, 2012) and 7T MRI (Downes & Pouratian, 2013) to assist with understanding the complicated nature of the relationship between motor and non-motor symptoms.

While the difficulties inherent in controlling for the effects of medications in PD research have already been outlined, it is recommended that future research seek
to mitigate these effects as much as possible. Drug naïve, de-novo people with PD, and people who have been temporarily taken off all anti-parkinsonian medications for the purpose of a status review prior to DBS for example, may provide valuable research opportunities.
References


*Current Opinions in Neurology, 26*, 339-344. doi: 10.1097/WCO.0b013e328363304c


Desmond, D., & MacLachlan, M. (2005). The factor structure of the Hospital Anxiety and Depression Scale in older adults with acquired amputations:
A comparison on four models using confirmatory factor analysis.

*International Journal of Geriatric Psychiatry*, 20, 344-349.


Leenders, K., Salmon, E., Tyrrell, P., Perani, D., Brooks, D., Sager, H…
Frackowiak, R. (1990). The nigrostriatal dopaminergic system assessed
in vivo by positron emission tomography in healthy volunteer subjects
and patients with Parkinson’s disease. Archives of Neurology, 47, 1290-
1298.

Leentjens, A., Dujardin, K., Marsh, L, Richard, I., Starkstein, S., & Martinez-Martin,
study of the Hamilton Anxiety Rating Scale, the Beck Anxiety
Inventory, and the Hospital Anxiety and Depression Scale. Movement

Leentjens, A., Dujardin, K., Marsh, L., Martinez-Martin, P., Richard, I., Starkstein,
… Goetz, C. (2008). Anxiety rating scales in Parkinson’s disease:
doi: 10.1002/mds.22233


Neurobehavioral Relationships in the Basal Ganglia in F. Barrios and C.
Bauer (Eds.) Basal Ganglia: An Integrative Review. InTech. doi:
10.5772/55227


Combined effect of age and severity on the risk of dementia in


Mak, E., Zhou, J., Tan, L., Au, W., Sitoh, Y., & Kandiah, N. (2013). Cognitive deficits in mild Parkinson’s disease are associated with distinct areas of
grey matter atrophy. *Journal of Neurology, Neurosurgery and Psychiatry*, published online. doi: 10.1136/jnnp-2013-305805


