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Nonpharmacological Interventions for Mild Cognitive Impairment in Parkinson's Disease

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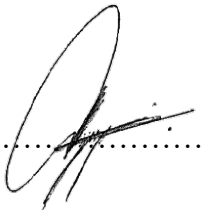
DECLARATION

To the best of my knowledge and belief this thesis contains no material previously published by any other person except where due acknowledgement has been made. This thesis contains no material which has been accepted for the award of any other degree or diploma in any university.

Signature: 

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STATEMENT OF CONTRIBUTION

The primary researcher (B.J.L) conceived, designed, and executed the research contained in this thesis. B.J.L collected all data for Study 1 and 2, while fellow PhD candidates (A.R.J and L.B) assisted with data collection for Study 3. B.J.L designed, implemented, and conducted all statistical analyses in this thesis. Supervisory researchers (A.M.L and N.G) provided advice when conceiving and designing the research, reviewed several drafts of each chapter, and a final draft of the completed thesis. All written content in this thesis is the work and intellectual property of B.J.L.

CONTENTS

TABLES

FIGURES

ABSTRACT

Over the past 10 years, Parkinson's Disease (PD) has been increasingly recognised as a disorder encompassing a diverse range of motor and nonmotor symptoms (Marras & Chaudhuri, 2016; Williams-Gray et al., 2013). Recent studies have begun to subtype mild cognitive impairment (MCI) in PD (PD-MCI) and highlight the negative impact of cognitive deficits on quality of life (Goldman et al., 2015; Klepac, Trkulja, Relja, & Babić, 2008). There is currently limited evidence supporting pharmacological treatment for PD-MCI, which has directed the scientific community to explore the therapeutic potential of nonpharmacological interventions (cognitive training and non-invasive brain stimulation) for cognition in PD (Hindle, Petrelli, Clare, & Kalbe, 2013). A significant proportion of people with PD-MCI progress to PD-Dementia (Janvin, Larsen, Aarsland, & Hugdahl, 2006). It is therefore important that researchers increase their understanding of PD-MCI and examine the potential of interventions for alleviating and potentially halting cognitive impairment in PD.

Study 1 examined the prevalence and subtypes of MCI in an Australian sample of people with PD. Seventy participants with PD completed neuropsychological assessments of their cognitive performance, using the Movement Disorder Society (MDS) Task Force Level II diagnostic criteria for PD-MCI. A cut-off score of less than one standard deviation (SD) below normative data determined impaired performance on a neuropsychological test. Of 70 participants, 45 (64%) met Level II diagnostic criteria for PD-MCI. Among those with PD-MCI, 42 (93%) were identified as having multiple domain impairment (28 as amnestic multiple domain and 14 as nonamnestic multiple domain). Single domain impairment was less frequent (2 amnestic / 1 nonamnestic). Executive function, attention/working memory, and memory were the most frequently impaired domains (> 60% of participants). Statistically significant ($p < .005$) differences were found between the PD-MCI and Normal Cognition groups, across all cognitive domains. The results

from Study 1 indicate that multiple domain cognitive impairment was more frequent than single domain impairment in an Australian sample of people with PD. However, PD-MCI is heterogeneous and current prevalence and subtyping statistics may be an artefact of variable application methods of the criteria (e.g., cut off scores and number of tests). Future longitudinal studies refining the criteria will assist with subtyping the progression of PD-MCI, while identifying individuals who may benefit from pharmacological and nonpharmacological interventions.

Study 2 examined cognitive training and non-invasive brain stimulation interventions for improving cognition in Parkinson's disease (PD). An extensive search was conducted of published and unpublished studies in online databases. Studies were selected if they were controlled trials examining standard (not individualised) or tailored (individualised) cognitive training, repetitive transcranial magnetic stimulation (rTMS), or transcranial direct current stimulation (tDCS) in PD, with outcomes measured by standardised neuropsychological tests. 14 controlled trials met inclusion criteria. The only controlled trial of tDCS did not provide sufficient data for inclusion. For executive function, the pooled effect size (Hedges' *g*) for cognitive training (standard and tailored combined) was small ($g = 0.42$) but statistically significant (95% CI 0.15 to 0.68). The pooled effect for standard cognitive training (alone) was medium ($g = 0.51$) and statistically significant (95% CI 0.16 to 0.85). For attention/working memory, small pooled effect sizes were found when combining standard and tailored cognitive training ($g = 0.23$; 95% CI 0.02 to 0.44) and for standard cognitive training alone ($g = 0.29$; 95% CI 0.04 to 0.53), both statistically significant. For memory, small but statistically significant pooled effect sizes were found when combining standard and tailored cognitive training ($g = 0.33$; 95% CI 0.06 to 0.59) and for standard cognitive training alone ($g = 0.35$; 95% CI 0.03 to 0.66). The results suggest that standard and tailored cognitive training may improve executive function, attention/working memory, and memory in PD. Future studies must adopt randomised controlled trial designs to explore the therapeutic potential of these interventions.

Study 3 compared the efficacy of cognitive training, transcranial direct current stimulation (tDCS), cognitive training + tDCS for improving cognition in people with PD-MCI. Participants were included if they met MDS Task Force Level

II criteria for PD-MCI. Participants (N = 42) were randomly allocated to one of six groups: (1) Standard Cognitive Training, (2) Tailored Cognitive Training, (3) tDCS, (4) Standard Cognitive Training + tDCS, (5) Tailored Cognitive Training + tDCS, or (6) a control group. Interventions lasted 4-weeks and participants' neuropsychological performance was measured at baseline, post-intervention (Week 5) and follow up (Week 12). While controlling for moderator variables (e.g., education, disease duration), Generalized Linear Mixed Models (GLMMs) were used to analyse outcomes. Compared to the control group: (1) executive function significantly improved in the Standard Cognitive Training + tDCS ($p < .001$) and Tailored Cognitive Training + tDCS ($p = .024$) groups, (2) attention/working memory significantly improved in the tDCS ($p = .039$) and Standard Cognitive Training + tDCS ($p = .028$) groups, (3) memory significantly improved in the tDCS ($p < .001$) and Tailored Cognitive Training + tDCS ($p < .001$) groups, (4) language significantly improved in the Standard Cognitive Training + tDCS ($p = .008$) and Tailored Cognitive Training + tDCS ($p < .001$) groups, (5) activities of daily living improved in the Standard Cognitive Training ($p < .001$) and Standard Cognitive Training + tDCS ($p = .014$) groups and (6) quality of life improved in the Standard Cognitive Training ($p = .003$) and Tailored Cognitive Training ($p = .016$) groups. Although sample size was small within groups, these preliminary results suggest that cognitive training, tDCS, and cognitive training combined with tDCS may improve cognition, activities of daily living, and quality of life in people with PD-MCI.

Overall, this research identified that a significant proportion of people with PD meet formal diagnostic criteria for PD-MCI. Cognitive impairment is extremely heterogeneous in PD and involves deficits across all cognitive domains. Earlier studies examining the potential of nonpharmacological interventions, such as cognitive training and non-invasive brain stimulation, were limited by methodology (i.e., lack of controlled designs). Combined with the findings of this research, however, there is increasing evidence to suggest that cognitive training, tDCS, and cognitive training combined with tDCS may induce neural plasticity in people with PD-MCI, which leads to significant improvements in cognition. It is recommended that future studies build upon the preliminary findings from this research and continue to explore the potential of nonpharmacological interventions for improving cognition and quality of life for people with in PD and PD-MCI.

OVERVIEW OF THESIS

This thesis contains five chapters. Chapter 1 provides an overview of Parkinson's Disease (PD), motor and non-motor symptoms, as well as current treatment options. Chapter 1 also provides a brief review of mild cognitive impairment and cognitive function in healthy ageing and neurodegenerative disorders (e.g., PD and Alzheimer's Disease), followed by an introduction to nonpharmacological interventions (cognitive training and non-invasive brain stimulation) for mild cognitive impairment and mild cognitive impairment in PD.

Chapter 2 presents the results of Study 1, which describe the prevalence and subtypes of mild cognitive impairment in PD (PD-MCI). Study 1 applied the Movement Disorder Society (MDS) Task Force Level II diagnostic criteria for PD-MCI to an Australian sample of people with PD. The aim of Study 1 was to explore frequency differentials of PD-MCI subtypes at varying diagnostic cut off scores and provide recommendations for future studies administering the MDS criteria in PD.

Chapter 3 presents the results from Study 2, which begins with a review of all controlled and uncontrolled cognitive training and non-invasive brain stimulation studies for cognition in PD. Following this, Study 2 presents the results of the first meta-analysis of all controlled cognitive training and non-invasive brain stimulation studies for cognition in PD. The aim of Study 2 was to summarise the current therapeutic potential of nonpharmacological interventions for cognition in PD and the implications of the findings for future clinical trials.

Chapter 4 presents the results from Study 3, which was the first randomised controlled trial of standard cognitive training, tailored cognitive training, transcranial direct current stimulation (tDCS), standard cognitive training + tDCS, and tailored cognitive training + tDCS for PD-MCI. Previous studies had examined the potential of these interventions individually, but none had combined these interventions in a

randomised controlled trial in PD-MCI. The aim of Study 3 was to investigate which intervention was most efficacious for improving cognition, activities of daily living, and quality of life for PD-MCI.

Chapter 5 provides a general discussion of the findings from this thesis and integrates the findings within the context of current research. Chapter 5 concludes with recommendations for future prevalence and interventional studies examining PD-MCI and with a few final words to close this thesis.

CHAPTER 1 Mild Cognitive Impairment in Parkinson's Disease

1.1 Introduction

Most developed countries are experiencing significant demographic changes, with increasingly large proportions of their population entering older age groups (World Health Organisation, 2015). Parkinson's Disease (PD) predominantly affects individuals over the age of 50 and with an ageing population, the number of people with PD is expected to rise (Dorsey et al., 2007). Following diagnosis people with PD live approximately 7 to 14 years, but increasing age and presence of dementia are associated with a decreased rate of survival (Macleod, Taylor, & Counsell, 2014). During this time, people with PD experience a range of motor and non-motor symptoms (e.g., mild cognitive impairment) that are heterogeneous and negatively impact the health and quality of life of the individual and their family (Aarsland et al., 2010; Marras & Chaudhuri, 2016; Muslimović et al., 2008). It is therefore of paramount importance that researchers explore all avenues of pharmacological treatments and nonpharmacological interventions that may have the potential to alleviate motor and nonmotor symptoms, and improve quality of life for people with PD.

This chapter is divided into two sections. The first half provides context for this research and includes a brief overview of PD, its aetiology, epidemiology, clinical presentation, and current treatments. The second half of the chapter focuses on cognition and mild cognitive impairment in PD, by providing an overview of mild cognitive impairment in healthy and PD populations, followed by neural and cognitive plasticity in older adults and neurodegenerative disorders (e.g., Alzheimer's disease [AD] and PD). This chapter closes with a brief review of the therapeutic potential of nonpharmacological interventions for mild cognitive impairment and PD.

1.2 Nosology of Parkinson's Disease

PD is classically defined as a member of the *parkinsonism* group of movement disorders and is characterised by four cardinal motor symptoms: postural instability, rigidity, rest tremor, and bradykinesia (Calne, 2005). Research over the past two decades has led to a profound development in our understanding of PD, with increasing knowledge of nonmotor symptoms, discovery of biomarkers and their role in disease progression, as well as recognition that neural degeneration may precede clinical manifestation of motor symptoms (Berg et al., 2014). This increase in our understanding has led to a proposal for a new definition of PD (see Berg et al., 2014). For the purpose of the current research, however, the classical definition of PD as a movement disorder will be maintained and applied throughout this thesis.

1.3 Aetiology

Most cases of PD are described as *idiopathic* meaning the causative factor is unknown (Bartels & Leenders, 2009). However, post-mortem studies provide substantial evidence that almost all people with PD experience a death of dopaminergic cells in the substantia nigra pars compacta (SNc), which results in a severe loss of dopamine across multiple brain circuits (Bartels & Leenders, 2009). Dopamine depletion impacts several cortical circuits (e.g., motor, limbic, cognitive) and their associated behavioural representations (Alexander & Crutcher, 1990). The motor circuit is most predominantly impacted by the loss of dopamine and is associated with the development of motor symptoms (Lewis & Barker, 2009). Large genome wide association studies also provide evidence linking genetic abnormalities and the onset of PD (Collins, Cummins, & Barker, 2015; Kasten & Klein, 2015). Specifically, two recent studies identified an association between a mutation of the glucocerebrosidase gene and earlier age onset of PD (Lill et al., 2015; Nalls et al., 2015). The worldwide genetic risk of PD has demonstrated poor clinical prediction of future diagnosis, however, more studies are providing consistent evidence of genetic abnormalities that are associated with the aetiology of PD (Darweesh et al., 2016). Overall, there is a current understanding that PD is individually heterogeneous and the consequence of several neurotransmitter and genetic abnormalities, yet advancing age remains the dominant risk factor for PD (Collins et al., 2015).

1.4 Epidemiology

PD is the second most common neurodegenerative disorder, following AD, and affects individuals across developed and developing nations (De Lau & Breteler, 2006). Meta-analytic evidence indicates that the prevalence of PD increases with age and is associated with minor gender and geographical differences (Pringsheim, Jette, Frolkis, & Steeves, 2014). Pringsheim (2014) and colleagues reported that the global prevalence of PD steadily increases from 41 people (per 100,000) within 40 to 49 years of age, to 1903 people at 80 years and older. The incidence of PD among women was less than among men, however, this was only prevalent for individuals aged 50 to 59 years. Compared to people from North America, Europe, and Australia the prevalence of PD was less among those from Asia, but only between 70 to 79 years (Pringsheim et al., 2014). In Australia, 67,000 people were living with PD in 2011 and more than 80% of those individuals were over the age of 65 (Access Economics, 2011). Each day in Australia there are approximately 30 people diagnosed with PD and this figure will likely increase with the ageing population (Access Economics, 2011). Although clinical (compared to pathological) diagnoses are less accurate at correctly diagnosing people with PD and may falsely inflate prevalence statistics (Hughes, Daniel, Kilford, & Lees, 1992), there is considerable evidence to indicate that the prevalence of PD is relatively consistent across all main geographical locations and will increase with the ageing population.

1.5 Clinical Presentation

1.5.1 Diagnosis

The United Kingdom Parkinson's Disease Society Brain Bank Clinical Diagnostic Criteria has been used as the predominant diagnostic tool for PD (Bartels & Leenders, 2009). The UK criteria state that in conjunction with a response to levodopa medication, a minimum of two from three motor symptoms (tremor, bradykinesia, rigidity) must be present to satisfy a clinical diagnosis of PD (Hughes et al., 1992). However, the Movement Disorder Society (MDS) recently published updated criteria for clinical diagnosis of PD, which involve an extensive clinical examination and several diagnostic stages with multiple inclusion and exclusion

criterion (Postuma et al., 2015). The MDS-PD criteria applies the following stages to determine a diagnosis of PD:

1. Establish if an individual has parkinsonism, defined as presence of bradykinesia in combination with either rest tremor, rigidity, or both.
2. Following a positive diagnosis of parkinsonism there must be an absence of absolute exclusion criteria, for example:
    i. Dementia, aphasia, normal dopaminergic system, or no response to levodopa therapy.
3. Following exclusion criteria the individual must meet two supportive criteria:
    i. A clear and dramatic response to dopaminergic therapy
    ii. Marked on/off fluctuations associated with dopaminergic therapy and worsening of parkinsonian symptoms during wearing off stages
4. Following the supportive criteria there must be no presence of potential red flags that may compromise an accurate diagnosis of PD, for example:
    i. Absence of motor symptoms or common nonmotor symptoms, autonomic failure, or presence of bilateral symmetric parkinsonism.

As noted by the authors, however, there is currently no scientific method available to ensure full diagnostic certainty of PD during life, with up to 95% of people having their diagnosis confirmed via autopsy (Postuma et al., 2015; Rajput, Rozdilsky, & Rajput, 1991). Nonetheless, the MDS-PD diagnostic criteria provide a thorough assessment of motor symptoms associated with parkinsonism and extensive inclusion and exclusion criteria to increase certainty in future diagnoses of PD.

1.5.1 Motor Symptoms

As previously noted, rest tremor, rigidity, bradykinesia, and postural instability/gait disturbance are the four cardinal motor symptoms of PD (Pagonabarraga, 2010). These symptoms normally present as unilateral and remain most severe on this side throughout the disease course (Haaxma et al., 2010). Tremor is identified as involuntary movements in the limbs and (less frequently) in the lips and jaw (Carr, 2002). Rigidity is a tensing and stiffness that is experienced throughout the muscles of the body (Bartels & Leenders, 2009). The stiffness and tensing associated with rigidity often causes irregular movements and an inability to

complete continuous actions. As hallmark feature of PD, bradykinesia is characterised by a slowness in initiating movements and an overall reduction in the speed and amplitude of movement (Pagonabarraga, 2010). Clinically manifested as short shuffling steps, postural instability/gait disturbance limits an individual's ability to move through their environment (specifically narrow spaces), and increases the probability of falls and associated injuries (Hanakawa et al., 1999). Although specific symptoms (i.e., tremor) are frequently occurring, PD is heterogeneous and motor subtypes have been developed in an attempt to account for the variability in severity and presentation of motor symptoms. These subtypes are known as tremor-predominant or postural instability/gait disorder (PIGD)-predominant (Lewis et al., 2005). Research suggests that rigidity and bradykinesia worsen over the disease course, whereas tremor severity may remain stable (Jankovic, 2008).

The Hoehn and Yahr scale is a frequently used measure of severity of PD progression (Goetz et al., 2004; Maetzler, Liepelt, & Berg, 2009). The Hoehn and Yahr scale describes five stages of PD: Stage 1, the person with PD has slowness of movement and unilateral tremor and rigidity. At Stage 2, there is an increase in slowness of movement, combined with a loss of facial expression and bilateral tremor and rigidity. At Stage 3, the most dominant symptoms increase in severity combined with a loss of balance. At Stage 4, severity of motor symptoms progress and the person with PD may lose physical independence, and at Stage 5 the individual will likely be limited to a wheelchair or be bedridden (Goetz et al., 2004). It is also important to note that research has identified 'mild parkinsonian signs' defined as subtle features of the motor symptoms that do not meet a formal diagnosis of PD, but precede onset and stage one of the disease (Louis & Bennett, 2007; Mahlknecht, Seppi, & Poewe, 2015).

1.5.1.1 Treatments for Motor Symptoms. Anti-parkinsonian medications are the most common form of pharmacological treatment and reduce morbidity and improve motor symptoms in the early stages of PD (Chou, 2012; Fung, Herawati, & Wan, 2009). Levodopa is the most effective treatment option for motor symptoms of PD (Collins et al., 2015). Over the past 40 years, studies have demonstrated a significant reduction in the severity of motor symptoms following treatment with levodopa (Fahn et al., 2004). However, there has been a long standing debate among

clinicians as to when levodopa treatment is most effective for people with PD (Fahn & Bressman, 1984). There are considerable side effects associated with levodopa therapy which negatively impact quality of life (Collins et al., 2015). Evidence suggests that people treated with levodopa for more than 4 to 6 years increase their risk of living with dyskinesias (involuntary movements) by up to 40% (Ahlskog & Muenter, 2001). Levodopa treatment is also accompanied by 'ON/OFF' periods, which result in significant beneficial effects that reduce motor symptoms (ON period), followed by significant worsening of motor symptoms (OFF period). The rollercoaster experience of ON/OFF periods has a detrimental impact upon an individual's quality of life (Rahman, Griffin, Quinn, & Jahanshahi, 2008). Those classified as 'young onset' (< 50 years of age) with the potential to live for several decades with PD, may consider postponing levodopa therapy to maintain their quality of life and only begin treatment when motor symptoms increase in severity (Collins et al., 2015). There is, however, an argument for starting levodopa treatment early in the disease course. A recent study demonstrated that compared to participants who delayed levodopa therapy for several years, participants who started treatment early reported significant improvements in functional and quality of life scores (PD Med Collaborative Group, 2014). Due to the diversity of motor symptoms in PD and the potential negative side effects that accompany levodopa therapy, the decision to begin this line of treatment must always be made through consultation with a physician or geriatrician.

Other common pharmacological treatments for motor symptoms include dopamine agonists and monoamine-oxidase B inhibitors (Collins et al., 2015). Dopamine agonists are frequently only used as a first treatment option in de novo (newly diagnosed) PD and to precede long-term treatment with levodopa (Watts, 1997). However, dopamine agonists have also shown efficacy as a supplemental therapy for people with advanced PD (Goetz, Blasucci, & Stebbins, 1999). The side effects associated with treatment with dopamine agonists are diverse and may include, impulse control disorders (e.g., gambling, hypersexuality, binge eating), hallucinations, nausea, and drowsiness (Chaudhuri & Schapira, 2009; Weintraub et al., 2010). Considering the potential consequences associated with the side effects (specifically, impulse control disorders) of dopamine agonists, regular clinical consultation and monitoring of treatment effects are recommended. Producing more

modest beneficial effects for motor symptoms than levodopa, MOAB inhibitors (selegiline and rasagiline) may also be prescribed as a therapy for PD (Marconi & Zwingers, 2014; Parkinson Study Group, 2004). In short, MOAB inhibitors prevent the breakdown of dopamine, which ensures increased levels of dopamine are maintained within cortical networks susceptible to dopamine depletion in PD (Collins et al., 2015). Few studies have examined the long-term efficacy of MOAB inhibitors, however, one study demonstrated slower disease progression over an 18-month period of treatment (Olanow et al., 2009). Generally, MOAB inhibitors are well tolerated with few side effects (Davis et al., 2013).

For people with advanced PD (HY stages 4 to 5), apomorphine, deep brain stimulation (DBS), and duodopa are potential avenues for treatment of motor symptoms (Worth, 2013). Apomorphine is a strong dopamine agonist and is delivered via either bolus injections or a subcutaneous pump (Martinez-Martin et al., 2015). For some individuals with PD, apomorphine may cause side effects including psychiatric episodes and nausea/vomiting (Collins et al., 2015). Unlike the previously described pharmacological treatments, DBS is a neurosurgical procedure and often provided to individuals who have developed a resistance to the beneficial effects of levodopa, but maintain severe motor symptoms (Volkmann et al., 2013). The DBS procedure involves insertion of an electrode into the brain to stimulate the subthalamic nucleus during 'OFF' periods of levodopa use, which alleviates dyskinesias in PD (Williams et al., 2010). As with most neurosurgical procedures there are considerable risks involved with DBS (e.g., infection, haemorrhage, electrode wire breakage), and treatment is often only recommended to people later in the disease course and following unsuccessful attempts at other treatment avenues (Benabid, Chabardes, Mitrofanis, & Pollak, 2009). Duodopa is a system that delivers a levodopa gel to the small intestine and has also shown efficacy in treating motor symptoms in people in the later stages of PD (Nyholm, 2012). However, the cost is considerable (AUD$60,000 per annum) and individuals usually need to explore other treatment options preceding an application for duodopa intervention (Collins et al., 2015).

1.5.2 Non-Motor Symptoms

PD is not confined to motor symptoms, with non-motor symptoms often impacting quality of life to a greater extent (Chaudhuri, Healy, & Schapira, 2006; Marras & Chaudhuri, 2016). Recent studies report at least one non-motor symptom in up to 100% of participant groups with PD (Kim et al., 2013; Krishnan, Sarma, Sarma, & Kishore, 2011). As with motor symptoms, nonmotor symptoms are heterogeneous and prone to fluctuations in severity (Khoo et al., 2013; Witjas et al., 2002). Non-motor symptoms can present during early stages of the disease course (Zis et al., 2015), such as olfactory dysfunction, which may develop among people with de novo PD (Chand & Litvan, 2007). Other non-motor symptoms include, depression, anxiety, impulse control disorders, pain, mild cognitive impairment, and dementia (den Brok et al., 2015; Marras & Chaudhuri, 2016; Mylius et al., 2015; Pfeiffer, 2016). Dementia and depression are recognised as the most detrimental nonmotor symptoms to impact quality of life among people with PD (Burn, 2002; Kadastik-Eerme et al., 2016). Meta-analytic results indicate that major depression is present in up to 17% of people with PD, minor depression in 22%, and dysthymia (mild depression) in 13% (Reijnders, Ehrt, Weber, Aarsland, & Leentjens, 2008). Preceded by mild cognitive impairment, up to 50% of people with PD progress to dementia within 10 years from diagnosis (Williams-Gray et al., 2013).

1.5.2.1 Treatments for Non-Motor Symptoms. Due to the heterogeneity of nonmotor symptoms in PD, there are often multiple treatment options available to alleviate the comorbidity of these symptoms. Serotonin reuptake inhibitors (SSRIs) are the most common and effective treatment for depression and have shown beneficial effects for anxiety in PD (Chen & Marsh, 2014; Weintraub, Moberg, Duda, Katz, & Stern, 2003). SSRIs increase serotonin levels in the brain and have been used extensively in healthy and psychiatric populations (Aarsland, Påhlhagen, Ballard, Ehrt, & Svenningsson, 2012; Troeung, Egan, & Gasson, 2013). Tricyclic antidepressants are also used to treat depression and anxiety in PD (Menza et al., 2009). There is currently no recommended treatment for impulse control disorders in PD. However, recent studies demonstrated that an anticonvulsant (topiramate) and antiepileptic (zonisamide) may benefit individuals experiencing impulse control disorders associated with PD (Bermejo, 2008; Bermejo, Ruiz-Huete, & Anciones, 2010). Olfactory dysfunction is common in up to 90% of people with PD, however,

there is currently no therapy to alleviate this symptom (Pfeiffer, 2016). There is also limited evidence to support treatments of mild cognitive impairment and dementia in PD (Burn, 2010). Preliminary studies report that cholinesterase inhibitors and memantine demonstrate beneficial but limited effects on mild cognitive impairment and dementia (Goldman & Weintraub, 2015). In addition, DBS has shown a worsening effect on cognitive function, despite the potential benefits of neurostimulation for motor symptoms (Rothlind et al., 2014). The current lack of empirical evidence to support pharmacological and surgical interventions for cognitive impairments in PD has led researchers to explore the therapeutic potential of nonpharmacological interventions, such as cognitive training and non-invasive brain stimulation (Hindle et al., 2013).

The next half of this chapter will briefly review mild cognitive impairment (MCI) in healthy ageing and in PD (PD-MCI), and provide an introduction to neural plasticity and nonpharmacological interventions for MCI.

1.6 Mild Cognitive Impairment

A proportion of older adults will experience cognitive decline, typically characterised by memory loss (Petersen, 2011).This such decline is normal and does not warrant clinical intervention (Petersen, 2011; Petersen et al., 1999). However, the theoretical framework of 'mild cognitive impairment' has been developed for people who experience more severe cognitive deficits (Winblad et al., 2004). The Diagnostic and Statistical Manual for Mental Disorders (DSM-5) describes 'mild neurocognitive disorder' as increased cognitive decline from a previous neuropsychological assessment, with the individual conscious of decline but the cognitive deficits not affecting activities of daily living (American Psychiatric Association, 2013). Throughout this thesis mild cognitive impairment (MCI) will be defined as a decline in cognition that does not interfere with an individual's daily activities, but is not normal for age or level of education (Gauthier et al., 2006).

MCI reflects the interim stage between normal cognitive functioning and probable AD or another dementia (Petersen, 2011). There are four subtypes of MCI

(amnestic single, amnestic multiple, non-amnestic single, and non-amnestic multiple) and classification depends upon the affected cognitive domain (memory, attention, visuospatial, executive function, and language; Petersen, 2011; Winblad et al., 2004). Amnestic single and multiple MCI are significant memory impairments that do not meet the criteria for a dementia diagnosis, the latter involving more than one domain deficit (Petersen, 2011). Non-amnestic single and multiple MCI are a decline within one or multiple cognitive domains other than memory (Petersen, 2011).

Petersen et al. (1999) proposed that impaired memory distinguished those with MCI and those without, suggesting MCI is a predictor of AD or dementia (Petersen et al., 1999). However, those with MCI demonstrate deficits in domains other than memory (Ribeiro, De Mendonca, & Guerreiro, 2006). Ribeiro and colleagues (2006) characterised domain deficits in MCI. Memory impairment was present for 63% of participants, visuospatial for 69%, and language for 34% (Ribeiro et al., 2006). Saunders and Summers (2011) examined non-memory cognitive deficits in MCI and found significant impairment in attention and executive functioning. These findings indicate that deficits in all cognitive domains, including memory, are representative of MCI.

Among older adults (> 65 years old), the prevalence rate of MCI is 10 – 30%, and amnestic is more common than non-amnestic (Ding et al., 2015; Manly et al., 2008; Pankratz et al., 2015; Petersen et al., 2010). MCI is more prevalent in men and among un-married people. Longer formal education is associated with a lower rate of MCI (Petersen et al., 2010). Evidence suggests that MCI is a heterogeneous condition, with participants with MCI performing significantly worse than controls on neuropsychological tests examining all cognitive domains (Nordlund et al., 2005). This poses a challenge for clinicians examining MCI characteristics as early predictors of AD/dementia (Nordlund et al., 2005; Saunders & Summers, 2011).

MCI is considered a precursor to AD or dementia. However, reported conversion rates vary (Rasquin, Lodder, Visser, Lousberg, & Verhey, 2005). Manly et al. (2008) conducted a large multi-ethnic study and found 22% of participants with MCI at baseline were diagnosed with AD at a 24 month follow-up. Participants with MCI were three times more likely to later demonstrate AD than healthy older adults

(Manly et al., 2008). Conversely, Petersen et al. (2005) reported a conversion rate to dementia of more than 90% for people with amnestic MCI, suggesting that dementia is the inevitable endpoint of MCI (Petersen et al., 2005). To clarify these differences, Mitchell and Shiri-Feshki (2009) calculated a meta-analytic annual conversion rate of 6.7% to dementia and 6.5% to AD, with the progression to dementia rarely exceeding 50% even after 10 years to follow up. These results suggest that a proportion of people living with MCI do not progress to AD or dementia.

Many older adults experience a range of cognitive deficits over extended or indefinite periods of time (Gauthier et al., 2006; Nordlund et al., 2005). Development of the MCI construct in the healthy non-clinical population has led to its application in people with neurodegenerative disorders, such as PD (Litvan et al., 2011). However, the progression of MCI and domains of impairment in PD are markedly different to the healthy population and those with AD (Besser et al., 2016; Caviness et al., 2007).

1.6.1 MCI in PD

PD-MCI is described as "cognitive decline that is not normal for age but with essentially normal functional activities … even at the time of PD diagnosis and prior to initiation of dopaminergic therapy" (Litvan et al., 2011, p. 1815). Controversy surrounds the use of 'MCI' as a construct in PD (Dubois et al., 2007; Poletti, Emre, & Bonuccelli, 2011). Some researchers suggest that due to the heterogeneity of PD-MCI and the proportion of individuals reverting back to normal cognition, diagnosing mild cognitive deficits in people with PD provides no current benefit to the individual and needs to be avoided, except for research purposes (Korczyn, 2016). There is increasing evidence, however, supporting PD-MCI as a stage of cognitive functioning often present at PD onset and preceding PD-Dementia (Barone et al., 2011; Chahine et al., 2016). Recent studies have also identified relationships between cognitive impairment and the asymmetric onset of motor symptoms (Lee et al., 2015), the postural instability/gait disturbance subtype (Kelly et al., 2015), and features of biomarkers that may predict onset of cognitive decline in PD (Delgado-Alvarado, Gago, Navalpotro-Gomez, Jiménez-Urbieta, & Rodriguez-Oroz, 2016; Matsumoto, 2015)

1.6.2 Epidemiology of PD-MCI

Among people with de novo and untreated PD, up to 10% demonstrate PD-MCI (Weintraub et al., 2015). In those with more advanced PD, Foltynie, Brayne, Robbins, and Barker (2004) found 36% of participants demonstrated cognitive impairments across four neurological subtypes: intact, frontostriatal, temporal lobe, and frontostriatal + temporal lobe. Three and half years later, a similar proportion of the participants met the criteria for MCI and 10% of the original participants had progressed to dementia (Williams-Gray, Foltynie, Brayne, Robbins, & Barker, 2007). The same healthy ageing MCI subtypes (amnestic single, amnestic multiple, nonamnestic single, and nonamnestic multiple) have also been reported for PD-MCI (Litvan et al., 2011; Petersen, 2011).

In a multicentre study of 1346 people with PD, Aarsland et al. (2010) found 26% had PD-MCI; with memory impairment in 13%, visuospatial impairment in 11%, and attention/executive function impairment in 10%. Nonamnestic MCI was the most common subtype (11%), in contrast to amnestic MCI being most common in healthy older adults (Aarsland et al., 2010). A recent systematic review found that 26% of nondemented people with PD also have MCI and nonamnestic single domain is more common than amnestic single domain (Litvan et al., 2011). Litvan et al. (2011) concluded that people with PD-MCI are at increased risk of progression to PD-Dementia.

1.6.3 PD-MCI as a Predictor of PD-Dementia

The predictive value of PD-MCI to PD-Dementia emphasises the need to diagnose PD-MCI early. Over a 5-year follow-up from initial PD diagnosis, Williams-Gray et al. (2009) reported that 17% of those with PD-MCI progressed to PD-Dementia at a rate four times the normal population. In a 4-year longitudinal study, Janvin, Aarsland, and Larsen (2005) found that 69% of nonamnestic single, 63% multiple domain, 40% amnestic single, and 20% with intact cognition had progressed to PD-Dementia. Irrespective of the high conversion rates, there is limited research into those PD-MCI subtypes which predict PD-Dementia (Barone et al., 2011). Research suggests that impaired executive functions, verbal fluency, and visuospatial/language abilities are predictors of PD-Dementia (Hobson, Meara, &

Evans, 2013; Janvin et al., 2005; Levy et al., 2002; Mahieux et al., 1998; Ramirez-Ruiz, Junque, Martí, Valldeoriola, & Tolosa, 2007). It is estimated that up to 80% of people are affected by dementia, with male gender associated with increased risk of dementia, and it has been identified as the most frequently associated symptom of increased mortality in PD (Aarsland, Zaccai, & Brayne, 2005; Cereda et al., 2016; Macleod et al., 2014; Reid, Hely, Morris, Loy, & Halliday, 2011).

1.6.4 Heterogeneity of PD-MCI

PD-MCI can be classified as four subtypes (amnestic single, amnestic multiple, nonamnestic single, and nonamnestic multiple), reflecting deficits across the five cognitive domains: memory, attention, language, visuospatial, and executive functions (Kehagia, Barker, & Robbins, 2010; Muslimovic, Schmand, Speelman, & De Haan, 2007). Muslimovic et al. (2007) conducted a meta-analysis examining patterns of cognitive impairment in people with PD. They concluded that, although changes in cognitive functioning are subtle, the first impaired domain may dictate the course of cognitive impairment (Muslimovic et al., 2007). The heterogeneity of PD-MCI adds to the diagnostic complexity for clinicians and researchers, which has led to the development of standardised diagnostic criteria (Litvan et al., 2012; Verleden, Vingerhoets, & Santens, 2007).

1.6.5 Diagnostic Criteria for PD-MCI

Neuropsychological test batteries have been used to identify cognitive impairments in PD (Barone et al., 2011). However, administration often varies (limiting external validity) and the use of generic measures in PD reduces reliability of results (Barone et al., 2011). Mamikonyan et al. (2009) examined the Mini-Mental Status Examination's (MMSE) ability to assess MCI in participants with PD. Thirty percent of participants with PD had MCI across memory, attention, and executive function domains. However, the same participants were classified as having 'normal' cognitive functioning according to the MMSE criteria (Mamikonyan et al., 2009). Although the MMSE is the most widely used measure of global cognitive impairment, these results highlight the need for standardised PD cognitive assessments and diagnostic criteria (Mamikonyan et al., 2009).

Diagnostic practise was to classify a person with PD-MCI if their performance on a neuropsychological test was 1.5 standard deviations (SDs) below the normative mean for that test (Barone et al., 2011). However, Litvan et al. (2011) suggests that PD-MCI should not be solely diagnosed by a test score, but should be supported by self-reported changes in cognition. Due to heterogeneity in the pathology and neuropsychological measures of PD-MCI, the Movement Disorders Society developed standardised diagnostic criteria for people with PD who present with cognitive impairments (Litvan et al., 2012). The diagnostic criteria increases uniformity across research and clinical practice and the authors urge health professionals to validate the criteria in the PD-MCI population (Litvan et al., 2012). Recent studies have begun to examine the psychometric properties and diagnostic accuracy of the new criteria for PD-MCI (e.g., Cholerton et al., 2014). However, no study has applied the diagnostic criteria to an Australian sample of people with PD and further validation and refinement of the criteria is required.

1.6.6 Correlates of PD-MCI and Impact on Quality of Life

Older age, more severe PD, less years of formal education, late disease onset, apathy, and depression are associated with more rapid cognitive decline in PD (Dujardin, Sockeel, Delliaux, Destée, & Defebvre, 2009; Foltynie et al., 2004; Mamikonyan et al., 2009; Muslimović, Post, Speelman, & Schmand, 2005; Pai & Chan, 2001; Starkstein, Mayberg, Leiguarda, Preziosi, & Robinson, 1992). Presence of hallucinations and apathy are also associated with executive function impairments in PD-MCI (Kulisevsky, Pagonabarraga, Pascual-Sedano, García-Sánchez, & Gironell, 2008).

MCI impacts activities of daily living and quality of life in people with PD (Lawson et al., 2016; Litvan et al., 2012; van Uem et al., 2016) Rosenthal et al. (2010) examined the functional impact of cognitive deficits on activities of daily living in PD-MCI and PDD, and found impaired activities of daily living in both groups. Klepac et al. (2008) examined the relationship between health-related quality of life and cognitive performance in people with PD. Participants with better performance on measures of executive and visuospatial functions, visual attention/memory, and global cognitive performance reported a better health-related

quality of life (Klepac et al., 2008). This suggests that cognitive deficits are associated with poorer activities of daily living and quality of life in PD (Klepac et al., 2008; Rosenthal et al., 2010).

1.7 Neural Plasticity

At the age of 65, adults experience a decline in behavioural and cognitive function (Yan, 2000). The importance of neural plasticity is most apparent for this cohort (Cai, Chan, Yan, & Peng, 2014). Neural plasticity is the central nervous system's (CNS) adaption of anatomical structures (neurons, glial cells, synapses, and blood vessels) and physiological processes following active engagement in cognitive and motor training (Ballantyne, Spilkin, Hesselink, & Trauner, 2008; Cai et al., 2014). By maintaining an active lifestyle, older adults strengthen their neural plasticity and experience less cognitive and physical decline (Stein & Hoffman, 2003). However, achieving 'successful ageing' is more challenging for those at risk of MCI and dementia (Kramer, Erickson, & Colcombe, 2006).

When an individual acquires new knowledge or skills in response to training, the information either strengthens the existing neural pathways and networks (building upon existing knowledge) or develops a new series of neural circuits and synapses (Wall, Xu, & Wang, 2002). During cognitive training an individual is exposed to repeated stimuli or required to practice cognition focused exercises (Cai et al., 2014). Neurons related to that exercise are simultaneously activated, which strengthens/modifies their firing in response to the learning experience (Cai et al., 2014). The strengthening of neuronal connections is known as synaptogenesis and is fundamental to neural plasticity (Ponti, Peretto, & Bonfanti, 2008). Synaptic changes in cerebral cortex activation occur in response to experience-dependent learning and have been demonstrated across the life-span into older age (Hill, Kolanowski, & Gill, 2011; Wall et al., 2002).

Experience-dependent neural plasticity (learning) is a complex process, influenced by age and pathology, which relies upon different cortical regions and the type of stimulus used (Cai et al., 2014; Johnson, 2003; Kim & Kim, 2014). Belleville

and colleagues (2011) investigated the potential of neural plasticity to reverse brain changes associated with MCI. Functional magnetic resonance imaging (fMRI) was used to monitor the pattern of neural activation among older adults with and without MCI, while completing a verbal memory task (Belleville et al., 2011). Patterns of increased activation after the memory training were observed in those participants with MCI (Belleville et al., 2011). These results suggest that the ageing and impaired brain maintains neural plasticity and the ability to learn.

1.7.1 Cognitive Capacity

Previous research demonstrates that individuals are able to learn and can improve their level of cognitive functioning as they age (Baltes & Mayer, 2001; Calero & Navarro, 2004; Verhaeghen, 2000). Cognitive capacity is described as the difference between an individual's baseline performance on a measure of cognition and their performance on the same measure after a period of cognition focused training/practise (Baltes, 1987). The potential of older adults with MCI to improve cognitive functioning following a cognitive training intervention has been demonstrated in "testing-the-limits" studies (Baltes, 1987; Sales-Galán, Meléndez-Moral, & Mayordomo-Rodríguez, 2013). "Testing-the-limits" of cognitive capacity involves three stages: (a) baseline performance, (b) baseline reserve capacity, and (c) developmental reserve capacity (Baltes, 1987). Testing-the-limits is comparable to pre-test assessment (baseline performance) – cognitive intervention (baseline reserve capacity) – post-test assessment (developmental reserve capacity).

Calero and Navarro (2004) examined whether older adults with MCI were able to learn and whether reduced cognitive capacity was a diagnostic marker of cognitive decline. Following an auditory learning intervention, both healthy participants and the participants with MCI improved their learning (Calero & Navarro, 2004). Furthermore, Sales-Galán et al. (2013) demonstrated that although healthy older participants performed better on a verbal learning test, those with MCI retained capacity for learning. It is fair to conclude that an individual's potential to learn is unequally reduced depending on their age and level of cognitive functioning (Calero & Navarro, 2004). Baltes and Mayer (2001) found that 17% of older adults aged 70 report cognitive impairment and the rate increases to 50% by the age of 90.

The effect of age is also compounded by its relationship with an increased rate of cognitive decline (Petersen, 2000). However, improvements in cognitive capacity are not eliminated as MCI and dementia progress.

1.7.2 Cognitive Capacity from MCI to AD

Research has demonstrated that older adults with MCI and *mild* AD can improve their performance in visuospatial abilities, executive functioning, and verbal fluency (Cai et al., 2014; Fernández-Ballesteros, Zamarrón, Tárraga, Moya, & Iñiguez, 2003). Fernández-Ballesteros et al. (2003) compared the performance of healthy older adults and those with MCI and AD, on the Verbal Memory Learning Potential (VMLt) training program to investigate differences in cognitive capacity. Results showed people in both MCI and AD groups improved their performance post-training (Fernández-Ballesteros et al., 2003). Fernández-Ballesteros et al. (2012) examined the contributions of age and pathology to learning performance in people with MCI and AD. Across all ages (55 to 102 years) and levels of pathology (MCI and AD), participants demonstrated learning after five trials of the VMLt (Fernández-Ballesteros et al., 2012). Although significant differences in learning ability were found between age and pathology groups, these results support the existence of cognitive capacity in older adults with a neurodegenerative disorder (Fernández-Ballesteros et al., 2012).

1.7.3 Cognitive Reserve in PD

Although there has been considerable research of cognitive capacity in healthy ageing, MCI, and AD, there is limited research in PD. Preliminary findings indicate that those with PD-MCI can improve their performance on neuropsychological tests after nonpharmacological training interventions, using cognitive reserve (Hindle, Martyr, & Clare, 2014; Poletti et al., 2011). However, it is important to distinguish between cognitive capacity and cognitive reserve. The former is inherent to the underlying biological process involving the strengthening and adaption of neuronal networks to increase learning ability (Cai et al., 2014). The latter is a description of the impact of lifelong experiences (e.g., education and occupational attainment) on an individual's cognitive resources, which result in their

ability to withstand greater pathology by relying on increased levels of cognitive reserve (Stern, 2012). Nonpharmacological interventions for PD-MCI include cognitive training (standard and tailored) and non-invasive brain stimulation (transcranial magnetic stimulation [TMS] and transcranial direct current stimulation [tDCS]), which rely upon cognitive capacity and reserve in people with PD (Hindle et al., 2013).

1.8 Nonpharmacological Interventions for MCI

The effectiveness of nonpharmacological interventions (cognitive training and non-invasive brain stimulation) for ameliorating cognitive decline has been explored (Kim & Kim, 2014; Walton, Mowszowski, Lewis, & Naismith, 2014). Research has demonstrated that older adults benefit from cognitive training and brain stimulation techniques (Berry et al., 2010; Kelly et al., 2014; Willis et al., 2006). However, the positive effect of cognitive training in older adults with MCI was comparable to that observed in controls (Martin, Clare, Altgassen, Cameron, & Zehnder, 2011; Zehnder, Martin, Altgassen, & Clare, 2009). This suggests that specific cognitive training provides no additional benefit to cognitive functioning than non-specific daily activities (e.g., physical exercise; Martin et al., 2011; Zehnder et al., 2009). Conflicting results have raised questions about the effectiveness of stimulation and compensation-focussed interventions for older adults with cognitive impairment.

Stimulation-focussed interventions involve the presentation of external novel stimuli that encourages neural plasticity by rewiring or strengthening synaptic connectivity in the brain (Kim & Kim, 2014). The external stimuli are either specific (visual, auditory, or motor) or non-specific (social interactions/physical activities; Kim & Kim, 2014). Optale et al. (2010) used specific visual and auditory stimuli, such as a computer-generated beach walk, to improve memory functions in older adults with MCI. Muscari et al. (2010) demonstrated that 12 months of non-specific endurance exercise training reduced age related cognitive decline in healthy older adults. Stimulation-focused interventions with and without specific stimuli can improve global and domain specific cognitive functioning, strengthening the brain's

existing synaptic networks to reduce the adverse effects of neurological ageing and neurodegenerative disorders (Kim & Kim, 2014).

Compensation-focussed interventions seek to improve frontal functions and/or enhance the brain's ability to compensate for impairments in cognitive domains (Kim & Kim, 2014). Compensatory techniques include meta-cognitive strategies, and executive control and speed of processing (Kim & Kim, 2014). The most common compensation-focused interventions are memory training in older adults (Kim & Kim, 2014). Memory training involves teaching participants new mnemonics to encode and organise information in a way that compensates for age-related memory decline. Kaci-Fairchild and Scogin (2010) showed that older adults improved their ability to remember names, faces, and locations of household items after completing an in-home memory enhancement program. The program emphasised the importance of subjective memory beliefs and objective memory abilities, thereby implementing a new mnemonic to compensate for memory deficits (Kaci-Fairchild & Scogin, 2010).

Depending on the cortical region for stimulation, non-invasive brain stimulation techniques (e.g., rTMS and tDCS) may also act as compensation-focussed interventions to alleviate cognitive deficits. The Scaffolding Theory of Ageing and Cognition proposes that as older adults experience a decline in cognition, the brain provides 'scaffolds' to compensate for inefficient function of specific cognitive abilities (Goh & Park, 2009). Predominantly occurring in the prefrontal cortices, scaffolds recruit secondary neural circuits to support the performance of the primary (but diminished) neural circuits (Park & Reuter-Lorenz, 2009). When targeting prefrontal cortices, rTMS and tDCS may therefore enhance the 'scaffolding' of secondary neural circuits by providing increased activation of these cortical regions as a compensation-focussed intervention for older adults with MCI.

Both stimulation and compensation-focused interventions improve cognitive functions in people with MCI. However, Kim and Kim (2014) suggest that merging the stimuli mechanisms from stimulation interventions with the cognitive needs of compensation interventions will improve participant outcomes to a greater extent.

Tailoring cognitive training and non-invasive brain stimulation to strengthen the neural networks of a *specific* cognitive domain may result in improved cognition.

1.8.1 Cognitive Training and General Mental Stimulation for MCI

The lack of consensus regarding pharmacological treatment (e.g., cholinesterase inhibitors) for people with MCI suggests that cognitive training or general mental stimulation may be therapeutic options for those showing early signs of cognitive impairment (Teixeira et al., 2012). Cognitive training is a structured programme of tasks designed to target the use of specific cognitive domains, in an attempt to improve cognitive functioning through repeated training sessions (Kelly et al., 2014; Martin et al., 2011). General mental stimulation is described as non-specific activities (e.g., exercise, socialising) that improve cognitive functioning (Kelly et al., 2014). In a review of cognitive training in MCI and AD, Mowszowski, Batchelor, and Naismith (2010) concluded that, for people with MCI, cognitive training has the potential to improve cognitive functioning and act as a therapeutic technique to delay progression of cognitive decline. Tappen and Hain (2014) compared an in-home cognitive training program with general mental stimulation of a life story interview. Only participants who completed the cognitive training program demonstrated improvements in cognitive functioning that were specifically related to the trained domain (Tappen & Hain, 2014). These results suggest that specific cognitive training is more effective than general mental stimulation at improving cognitive functioning (Tappen & Hain, 2014).

1.8.2 Brain Stimulation for MCI and AD

Transcranial magnetic stimulation (TMS) is a non-invasive tool which employs an electromagnetic coil to excite or inhibit cortical functions (Barker, Jalinous, & Freeston, 1985; Guse, Falkai, & Wobrock, 2010). In a systematic review, Guse et al. (2010) examined studies using high frequency rTMS to induce long-term potentiation (LTP) of neuronal firing to improve cognitive function in healthy participants and those with MCI. High-frequency rTMS (10 to 20 Hz) applied over the left dorsolateral prefrontal cortex significantly improved executive function, learning, and memory in people with MCI (Guse et al., 2010). The improvement in cognition was greater in MCI compared to healthy participants (Guse et al., 2010).

These results support the use of brain stimulation to improve cognitive function in people with MCI and provide evidence of neural plasticity in this population (Cai et al., 2014).

The limited benefits of pharmacological treatments for people with MCI are mirrored in AD (Birks, 2006; Nardone et al., 2012). This has led researchers to investigate the effectiveness of rTMS and tDCS for modifying and delaying cortical degeneration in people with AD (Nardone et al., 2012). tDCS can be used to modulate neuronal activity by delivering low intensity (1 mA or 2 mA) electrical currents to a specific cortical region (Creutzfeldt, Fromm, & Kapp, 1962; Nardone et al., 2012). Anodal tDCS and high frequency rTMS increase, whereas, cathodal tDCS and low frequency rTMS decrease cortical excitability. Both rTMS and tDCS impact cortical excitability, although it is not known if one method induces greater long-term change (Nardone et al., 2012; Nitsche & Paulus, 2000; Pascual-Leone et al., 1998).

To compare the long-term effect of high and low frequency rTMS on cognitive function, Ahmed, Darwish, Khedr, and Ali (2012) applied bilateral trains of contrasting rTMS frequencies over the left dorsal lateral prefrontal cortex of people with AD. Those who received high frequency rTMS improved in global cognitive functioning and activities of daily living, significantly more than the low frequency group (Ahmed et al., 2012). These improvements were maintained at a three-month follow up assessment (Ahmed et al., 2012). Boggio et al. (2009) compared the effect of anodal tDCS over the left temporal cortex and the left dorsal lateral prefrontal cortex in people with mild and moderate AD. Stimulation over both cortical areas led to significant improvement in visual recognition memory (Boggio et al., 2009). However, the authors did not report any long-term effect (Boggio et al., 2009). Bentwich et al. (2011) investigated whether combining high-frequency rTMS interlaced with cognitive training (rTMS-COG) improved cognitive functioning in people with AD. Participants demonstrated improved cognitive functioning after a six-week intervention and the improvements were maintained for 4.5 months (Bentwich et al., 2011). The authors concluded that rTMS-COG is an effective treatment for AD (Bentwich et al., 2011). The previous studies demonstrate that

noninvasive brain stimulations improve cognitive functioning in older adults with a neurodegenerative disorder.

1.8.3 Nonpharmacological Interventions for PD

The efficacy of nonpharmacological interventions for people with PD and PD-MCI is ambiguous (Hindle et al., 2013). Initial research suggests that cognitive training interventions may reduce the rate of cognitive decline for people with PD-MCI and PDD (Burn, 2010; Kehagia et al., 2010). Studies using rTMS and tDCS have reported positive, but variable, effects on cognitive functioning in people with PD and there is a lack of consensus regarding the administration methods for brain stimulation in PD (Benninger et al., 2010; Hindle et al., 2013). Following a review of the prevalence and subtypes of MCI in PD, chapter 3 will provide a thorough review of all controlled and uncontrolled trials of cognitive training and non-invasive brain stimulation for cognition in PD.

1.9 Chapter Summary

PD is a heterogeneous neurodegenerative disorder accompanied by many motor and nonmotor symptoms. Cognitive deficits are now increasingly recognised as a nonmotor symptom affecting a significant proportion of people with PD and these impairments impact activities of daily living and quality of life. Preliminary evidence suggests that nonpharmacological interventions, such as cognitive training and non-invasive brain stimulation, may benefit PD and PD-MCI (Hindle et al., 2013). Recent development of the MDS diagnostic criteria for PD-MCI (Litvan et al., 2012) provides future studies with recommendations for standardised assessment of cognition in PD, and may increase consistency across studies examining cognitive subtypes that may predict progression to PD-Dementia.

The next chapter reports prevalence and subtyping statistics of PD-MCI when applying the MDS criteria for cognitive impairment in PD.

CHAPTER 2 Study 1. Prevalence and Subtypes of Mild Cognitive Impairment in Parkinson's Disease[1]

2.1 Introduction

Parkinson's disease (PD) is now understood as a multifaceted neurodegenerative disorder presenting with heterogeneous motor and non-motor symptoms (Williams-Gray et al., 2013). Approximately 30% of people with PD experience cognitive impairment and up to 50% progress to PD-Dementia after more than 10 years (Cosgrove, Alty, & Jamieson, 2015; Litvan et al., 2011). Cognitive impairments in PD comprise four subtypes: amnestic single, amnestic multiple, nonamnestic single and nonamnestic multiple. The four subtypes reflect deficits across five cognitive domains: memory, attention/working memory, language, visuospatial, and executive functions (Kehagia et al., 2010; Muslimovic et al., 2007).

Several biological and epidemiological risk factors are associated with cognitive deficits in PD, with studies reporting cognitive impairment even at time of diagnosis (Pedersen, Larsen, Tysnes, & Alves, 2013; Williams-Gray et al., 2009). To standardise assessment, the Movement Disorder Society (MDS) Task Force developed new diagnostic criteria for PD-MCI (Litvan et al., 2012). Preceding the criteria, most studies adopted the method proposed by Petersen (2011) which specifies a decline in memory. However, PD-MCI is heterogeneous and many people demonstrate impairments across the spectrum of cognitive domains (Goldman et al., 2013). The MDS diagnostic criteria specifies the following guidelines for Level I

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(abbreviated assessment) and Level II (comprehensive assessment) categories of PD-MCI (Litvan et al., 2012):

A. Level I (abbreviated assessment)
    a. Impairment on a scale of global cognitive abilities validated for use in PD
    or
    b. Impairment on at least two tests, when a limited battery of neuropsychological tests is performed (i.e., the battery includes less than two tests within each of the five cognitive domains, or less that five cognitive domains are assessed).
B. Level II (comprehensive assessment)
    a. Neuropsychological testing that includes two tests within each of the five cognitive domains (i.e., attention and working memory, executive, language, memory, and visuospatial).
    b. Impairment on at least two neuropsychological tests, represented by either two impaired tests in one cognitive domain or one impaired test in two different cognitive domains.
    c. Impairment on neuropsychological tests may be demonstrated by:
        i. Performance approximately 1 to 2 SDs below appropriate norms
        or
        ii. Significant decline demonstrated on serial cognitive testing
        or
        iii. Significant decline from estimated premorbid levels.

Recent studies adopting the new MDS diagnostic criteria report variable results (Cholerton et al., 2014; Marras et al., 2013). These studies also applied varying diagnostic cut off scores and number and weighting of tests per cognitive domain, which may influence the reported prevalence of cognitive impairment in PD. The significant impact of cognitive impairment on quality of life for people with PD indicates that any standardised criteria developed for international use needs to be validated and examined across multiple populations of PD. To date, no study has applied the MDS criteria for PD-MCI to an Australian sample. This study provides a novel application of the MDS Task Force PD-MCI Level II diagnostic criteria to an Australian sample of people with PD. This study also examined the PD-MCI

frequency differentials at varying diagnostic cut off scores to explore subtype classifications and advance our understanding of cognitive impairments in PD.

2.2 Methodology

2.2.1 Research design

This study used a cross-sectional design to measure cognitive performance of people with PD. A cross-sectional design allowed the researcher to assess a large sample of participants with the new MDS Task Force diagnostic criteria for PD-MCI (Litvan et al., 2012). Neuropsychological assessments were completed at Curtin University's Neuroscience Laboratory between March and September, 2015.

2.2.2 Participants

2.2.2.1 Power analysis and sample size. Previous PD-MCI studies recruited between 72 and 139 participants (Cholerton et al., 2014; Goldman et al., 2013; Janvin et al., 2006; Marras et al., 2013; Sollinger, Goldstein, Lah, Levey, & Factor, 2010). However, most participants recruited for this study also completed Study 3 (Chapter 4). Therefore, it was necessary to determine the number of participants required for Study 3 to inform Study 2. Paris et al. (2011) and Naismith et al. (2013) found moderate to large effect sizes for cognitive outcomes (Cohen, 1992). An a priori power analysis for an analysis of covariance (ANCOVA) was calculated using G*Power (Faul, Erdfelder, Lang, & Buchner, 2007) and 54 participants with PD-MCI were required to detect moderate effects in Study 3 (power = .80, $\alpha = .05$). To reduce the impact of potential participant attrition on power, 90 participants with PD-MCI were targeted for recruitment.

2.2.2.2 Inclusion and exclusion criteria. Participants were adults (> 18 years of age) with PD and living in Western Australia. The following inclusion criteria were used: (1) diagnosed with idiopathic PD by a neurologist or geriatrician in accordance with the United Kingdom Parkinson's Disease Society Brain Bank Clinical Diagnostic Criteria and (2) a stable response to antiparkinsonian medication for a minimum period of 2 months and (3) cognitive deficits that do not interfere with functional independence. Exclusion criterion was presence of PD-Dementia to

ensure all included participants understood the purpose of the study and were able to provide informed consent.

2.2.3 Measures

Neuropsychological assessments were conducted in two phases. Participants were first screened over the telephone for the presence of dementia and then completed an extensive neuropsychological assessment at Curtin University. In accordance with the MDS Task Force Level II diagnostic criteria for PD-MCI, two measures were selected to assess each of the five cognitive domains (executive function, attention/working memory, memory, language, and visuospatial abilities) involved in PD-MCI (Litvan et al., 2012). The following measures have been recommended by the MDS Task Force for use in PD and were used to assess functioning across all cognitive domains.

2.2.3.1 Screening measures. The *Telephone Interview for Cognitive Status-30* (TICS-30) was used to assess cognitive functioning and presence of dementia over the telephone (Brandt, Spencer, & Folstein, 1988). Development of the TICS-30 was based on the 'gold standard' test of cognition, the Mini Mental State Examination (Folstein, Folstein, & McHugh, 1975). The TICS-30 contains eight items assessing orientation, mathematical skills, short-term memory, attention/working memory and language. Items include "What month of the year is this?", "Please spell the word WORLD backwards", and "What do people usually use to cut paper?". TICS-30 scores range 0 to 30 with the following severity ratings corresponding to the MMSE: 0 to 12 (severe cognitive impairment), 13 to 17 (mild cognitive impairment), and 18 to 30 (unimpaired cognitive ability). Participants were required to score 13 or higher to be included in the study (Fong et al., 2009). Although there is limited psychometric information for the TICS-30, it has a strong correlation (r = .80) with the MMSE (Fong et al., 2009).

2.2.3.2 Demographic questionnaire. Following telephone screening and preceding formal neuropsychological assessment, participants completed a demographic questionnaire. The demographic questionnaire asked participants to report their personal and health information, age, gender, disease duration (years),

and current daily levodopa dopaminergic medication dosage. Participants were asked to bring the completed questionnaire to their assessment.

2.2.3.2 Executive function. The Cambridge Neuropsychological Test of Automated Batteries (CANTAB™) *Stockings of Cambridge* (SOC) subtest was used to assess executive function. SOC is a spatial planning test based upon the Tower of London task (Lezak, Howieson, & Loring, 2012). SOC tests executive function skills such as simultaneous use of rule learning, planning, and execution. Participants were shown a computerised touch screen tablet which presented two horizontal displays of coloured balls sitting in stockings (see Figure 1). Participants were instructed to rearrange the balls in the lower display to match the configuration of balls in the upper display. The goal was to rearrange the coloured balls using the least number of moves, with task difficulty (number of moves) increasing as participants progressed. Patterns completed within minimum moves was used as the outcome variable in this study (higher scores represent greater executive function). There is limited psychometric data for the CANTAB™ tests (Lezak et al., 2012), but the SOC subtest has shown modest test-retest reliability (r = .60) in older adults (Lowe & Rabbitt, 1998). Normative data was obtained from CANTAB™ software.

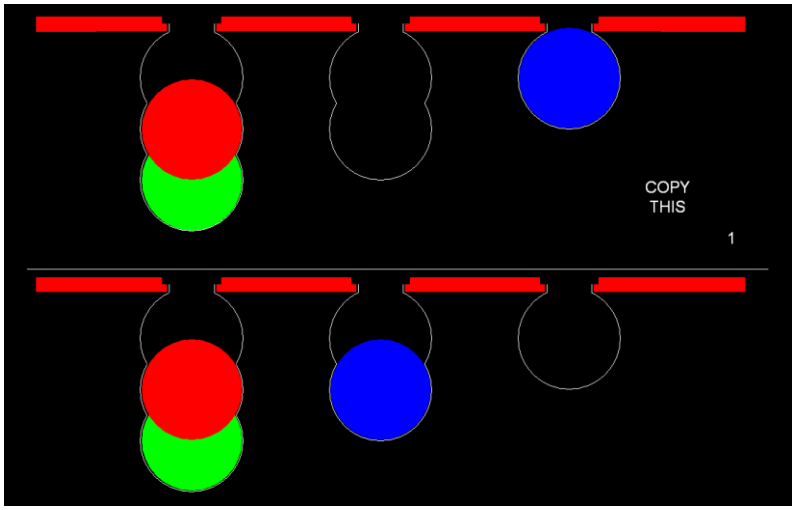

Figure 1. Example Activity from the Stockings of Cambridge Test.

The *Controlled Oral Word Association Task* (COWAT) was also used to assess executive function (Benton, 1968). The COWAT measures phonemic and semantic verbal fluency. The MDS Task Force recommend the use of only one

verbal fluency test to diagnose cognitive impairment, due to high correlations between similar tests (Litvan et al., 2012). Semantic verbal fluency has shown relative stability in people with PD-MCI compared to those with PD-Dementia (Kehagia et al., 2010; Williams-Gray et al., 2007). Phonemic verbal fluency was therefore used to measure executive function. Participants were given 60 seconds to provide as many words as possible beginning with a specified letter (e.g., F, A, or S). Prior to each trial, instructions were provided to ensure participants did not provide incorrect words (e.g., proper nouns, repetitions, variants of the same word). Total scores were calculated as the sum of correct words across trials with higher scores demonstrating greater verbal fluency (Lezak et al., 2012). The COWAT has shown high internal (r = .83) and test-retest (r = .74) reliabilities (Tombaugh, Kozak, & Rees, 1999), as well as high convergent validity (r = .72 to .81) with other verbal fluency tasks (Cohen & Stanczak, 2000). Furthermore, meta-analytic results show significant differences in verbal fluency performance between people with PD and healthy controls (Henry & Crawford, 2004). Impairment was assessed using normative data by Tombaugh et al. (1999).

2.2.3.3 Attention/working memory. The *Letter-Number Sequencing* (LNS) subtest from the Wechsler Adult Intelligence Scale-IV (WAIS-IV) was used to assess attention/working memory (Wechsler, 2008). The WAIS-IV includes 13 subtests and is used to measure general intellectual functioning in older adolescents and adults (16 to 89 years). For the LNS subtest, participants were read a randomised combination of letters and numbers (e.g., 6-F-2-B) and asked to recall the list in ascending order and numbers first (Wechsler, 2008). LNS contains 10 items with three trials per item and items were discontinued when a participant scored three incorrect responses in one item. Scores ranged from 0 to 30 with higher scores indicating greater attentional and working memory abilities. The LNS subtest has shown high internal consistency (r = .80 to .89) and adequate test-retest reliability (r = .70 to .79; Wechsler, 2008). When administered independently, the LNS subtest has shown sufficient specificity (Kaufman & Lichtenberger, 1999). Previous studies have used the LNS subtest to examine cognitive functioning in PD (Higginson et al., 2003; McKinlay, Grace, Dalrymple-Alford, & Roger, 2010). Raw and scaled scores were computed for each participant, with scaled scores compared to WAIS-IV normative data to establish degree of cognitive impairment (Wechsler, 2008).

Attention/working memory was also measured using the *Stroop (Colour-Word) Test* (Golden & Freshwater, 2002; Jensen & Rohwer, 1966; Stroop, 1935). The Stroop (Colour-Word) Test involves selective attention and inhibition, whereby participants are presented with an incongruent colour naming task (e.g., the word 'GREEN' printed in the colour BLUE). Participants were shown an A4 sheet of paper containing a set of 100 words arranged in five vertical columns (20 words per column). Participants were given 45 seconds to name what colour ink each word was printed in as they read down each column (Golden & Freshwater, 2002). Slow performance on this task demonstrates poor concentration, inhibition and attentional abilities (Lezak et al., 2012). Scores range from 0 to 100 and total scores were calculated as number of correct words in 45 seconds. The Stroop (Colour-Word) Test has shown adequate test-retest reliability (r = .73) and convergent validity (r = .55) with other attention tests (Golden, 1975; May & Hasher, 1998). Studies have found impaired colour-word performance in PD (Hanes, Andrewes, Smith, & Pantelis, 1996) and in people with deficits in prefrontal (dorsolateral and ventrolateral) cortices (Demakis, 2004). Scores were compared against normative data from Fisher, Freed, and Corkin (1990).

2.2.3.4 Memory. The *Hopkins Verbal Learning Test-Revised* (HVLT-R) was used to measure memory (Brandt & Benedict, 2001). The HVLT-R comprises 12 noun words drawn from three semantic categories (e.g., animals, dwellings, and precious stones). Participants were read the randomised list of words and asked to repeat the words they remembered in any order (Brandt & Benedict, 2001). Three consecutive trials were completed using the same list of words. Total scores were calculated as the sum of correct words across all trials, with higher scores representing greater retention. Benedict and Zgaljardic (1998) reported adequate test-retest reliability (r = .66) among older adults. In addition, adequate convergent validity (r = .60) was shown between the HVLT-R and the California Verbal Learning Test in AD (Lacritz, Cullum, Weiner, & Rosenberg, 2001). The HVLT-R has been used to assess memory impairment (Weintraub, Moberg, Culbertson, Duda, & Stern, 2004) and the relationship between impaired memory and motor symptoms in PD (Foster et al., 2010). Degree of memory impairment was compared to

normative data from Brandt and Benedict (2001) and Hester, Kinsella, Ong, and Turner (2004).

The *Paragraph Recall* subtest of the Rivermead Behavioural Memory Test (RMBT) was also used to assess memory (Wilson, Cockburn, Baddeley, & Hiorns, 1989). The RMBT was initially developed to examine memory impairment in people with acquired neurological damage (Cockburn & Keene, 2001) and contains 11 subtests measuring immediate and delayed recall abilities (Strauss, Sherman, & Spreen, 2006). During the Paragraph Recall subtest, participants were read a short story (5 to 6 lines) and asked to immediately recall the 'ideas/details' as they remembered them. This task has no time limit, although most participants provided details within 60 seconds following the story. Scores ranged 0 to 21 with higher scores demonstrating greater memory recall (Wilson et al., 1989). The total number of correct 'ideas/details' was used as the score for this outcome. There is limited psychometric information for the RBMT subtests, but the full battery has shown high internal consistency (Cronbach's $\alpha = .86$) and test-retest reliability ($r = .89$), as well as moderate convergent validity with other memory tests (Fennig, Mottes, Ricter-Levin, Treves, & Levkovitz, 2002; Man & Li, 2002). Pérez and Godoy (1998) found the RBMT correctly classified AD, older adults with cognitive complaints, epilepsy and controls at a rate of 72.5%. Paragraph recall tests have been successfully used to assess memory impairment in PD (Cummings, 1988; Taylor, Saint-Cyr, & Lang, 1986). Scores were examined against normative data from Wilson et al. (1989) and Strauss et al. (2006).

2.2.3.5 Visuospatial. The *Judgement of Line Orientation* (JLO) test measures orientation/spatial perception and was used to assess visuospatial abilities (Benton, Hamsher, & Sivan, 1994). The JLO test was initially developed to measure left versus right visual hemisphere superiority in people who were right hand dominant. The test is now used across many clinical groups including schizophrenia, AD, and PD (Finton, Lucas, Graff-Radford, & Uitti, 1998; Hardoy et al., 2004; Montse, Pere, Carme, Francesc, & Eduardo, 2001). Participants were shown a series of cards and asked to estimate the angles of lines on an upper card by comparing them to a set of numbered angled lines on a lower card. The JLO test comprises 30 items (one pair of angled lines per item) and is scored 0 to 30 (Benton et al., 1994). The following

scores represent visuospatial deficits: < 17 (severe impairment), 17 to 23 (mild impairment), and > 23 (no impairment). The JLO test has shown high internal (r = .90) and test-retest (r = .90) reliability (Benton et al., 1994; Qualls, Bliwise, & Stringer, 2000), as well as adequate convergent validity (r = .69) with WAIS-R visuospatial tests (Trahan, 1998). The JLO test has also been used to assessed impaired visuospatial abilities in PD (Montse et al., 2001). Normative data from Glamser and Turner (1995) and Ska, Poissant, and Joanette (1990) were used to interpret results.

The *Hooper Visual Organisation Test* (HVOT) was also used to measure visuospatial abilities (Hooper, 1983). Similar to the JLO test, the HVOT was originally developed to discriminate between people with and without cortical damage (Hooper, 1958). The HVOT is now often used to assess visuospatial deficits in AD and PD (Caselli et al., 2014; Cholerton et al., 2014). Participants were presented with a series of cards which contained common objects/animals that were cut into two or more illogical pieces. Participants were instructed: "*As you can see here, this is an object that has been cut into pieces. Tell me what you think the object would be if the pieces were put back together again.*" The HVOT includes 30 items with increasing ambiguity (Strauss et al., 2006). Scores range 0 to 30, with a score less than 23 indicative visuospatial impairment. The HVOT has shown high internal ($r \geq .80$) and test-rest (r = .86) reliabilities (Lezak, Howieson, & Loring, 2004; Lopez, Lazar, & Oh, 2003). Also, Ricker and Axelrod (1995) found that 48% of the variance in HVOT scores was accounted for by the WAIS perceptual subtests, supporting the HVOT as a valid measure of visuospatial abilities. Normative data from Tamkin and Jacobsen (1984) was used to interpret results.

2.2.3.6 Language. The *Boston Naming Test-Short Form* (BNT-Short Form) was used to assess language (Kaplan, Goodglass, & Weintraub, 2001). The BNT-Short Form is a revised 15-item version of the original 60-item test (Mack, Freed, Williams, & Henderson, 1992). Participants were shown a series of line drawings of objects of increasing difficulty, ranging from simple, high frequency vocabulary words (e.g., house) to rare words (e.g., sphinx). Scores range 0 to 15 with higher scores demonstrating greater language proficiency (Kaplan et al., 2001). Tombaugh and Hubiey (1997) reported adequate internal consistency (α = .49) for the BNT-

Short Form in people with AD. The BNT-Short Form has also shown high convergent validity with the full 60-item BNT (r = .72 to .82) and with the Visual Naming Test (r = .76 to .86) (Axelrod, Ricker, & Cherry, 1994; Tombaugh & Hubiey, 1997). The BNT has been used extensively in AD and PD research (Henry & Crawford, 2004; Henry, Crawford, & Phillips, 2004). Scores were compared against normative data by Fastenau, Denburg, and Mauer (1998).

Another test from the WAIS-IV battery, the *Similarities* subtest was used to assess language (Wechsler, 2008). The Similarities subtest assesses language and abstract reasoning, and participants were instructed as follows: "*Now I'm going to say two words and ask you how they are alike. For example, in what way are TWO and SEVEN alike?"* Instructions were read verbatim to each participant, with stimulus words increasing in difficulty (e.g., 'horse and tiger' to 'poem and statue') across the 18 items (Wechsler, 2008). Total scores range from 0 to 36 with higher scores representing greater language proficiency. The Similarities subtest showed high internal and test-retest reliabilities (r = .80 to .89; Wechsler, 2008), as well as sufficient subtest specificity when used independently (Kaufman & Lichtenberger, 1999). As with the LNS subtest, Similarities raw and scaled scores were computed for each participant, with scaled scores compared to WAIS-IV normative data to determine the degree of language impairment (Wechsler, 2008).

2.2.3.7 Global cognition. The *Parkinson's Disease – Cognitive Rating Scale* (PD-CRS) was used to assess global cognitive impairment (Pagonabarraga et al., 2008). The PD-CRS examines the full spectrum of cognitive functioning in PD, from cognitively intact to PD-MCI and PDD (Kulisevsky & Pagonabarraga, 2009). The PD-CRS contains nine items assessing attention, executive functions, verbal fluency/memory, visuospatial abilities and language. Examples include, word recall (memory) and copying a clock drawing (visuospatial). Total scores were calculated by summing individual item scores and recommended cut-offs suggest: < 64 (dementia), 64 to 82 (mild cognitive impairment) and > 81 normal cognition (Pagonabarraga et al., 2008). The authors report high internal consistency (α = .85) and the PD-CRS has shown strong discriminant validity (p < .001) when administered to healthy controls, cognitively intact PD, PD-MCI and PDD groups (Pagonabarraga et al., 2008).

The *Mini Mental State Examination* (MMSE) was also used as a measure of global cognition (Folstein et al., 1975). Designed to distinguish cognitive functioning between neurological and psychiatric patients (Folstein et al., 1975), the MMSE is the most widely used screening measure of global cognition. The test is attractive due to its brevity and ease in administration and scoring. The MMSE includes five items assessing orientation, immediate recall, attention/calculation, (slight) delayed recall and language (Strauss et al., 2006). Total scores range 0 to 30 and the following cutoffs were used: 0 to 9 (severe impairment), 10 to 20 (moderate impairment), 21 to 24 (mild impairment) and 25 to 30 (normal cognition; Folstein et al., 1975). This study calculated total scores using the serial 7s method by Strauss et al. (2006).

2.2.3.8 Premorbid intelligence. The *Australian version of the National Adult Reading Test* (AUSNART) was used to measure premorbid intelligence (Hennessey & Mackenzie, 1995). The AUSNART assesses an individual's ability to read a list of words that do not conform to the regular rules of reading (Hennessy & Mackenzie, 1995). For example, *coelacanth* is pronounced *see-luh-kanth*. Participants were instructed to pronounce each word on a series of cards and total scores were recorded as the number of errors (incorrectly pronounced words). Items were discontinued when a participant provided 12 incorrect responses within their previous 13 attempts. AUSNART scores were used to calculate premorbid intelligence using the Sullivan, Senior, and Scarcia (2000) regression equation:

$$110.15 - .48(\text{AUSNARTerr}) + 2.97(\text{Education}) - 3.01(\text{Sex})$$

where: AUSNARTerr : incorrect responses

Education : less than 9 years = 1; 9 to 10 years = 2; 11 to 12 years = 3; 13 to 15 years = 4; 16 years or more = 5

Sex : Male = 1; Female = 2

2.2.3.9 Functional independence. The *Unified Parkinson's Disease Rating Scale (section II)* was used to measure functional independence (Goetz et al., 2008).

The UPDRS-II includes 13 items that assess the impact of parkinsonian symptoms on an individual's ability to complete activities of daily living, independently. Items include: *"Over the past week, have you usually had problems dressing?"* and *"Over the past week, have you usually had trouble doing your hobbies or other things that you like to do?"* Each item is scored between '0 = Normal' and '4 = Severe'. Total scores were then computed into a summary index score by summing the 13 items and dividing the total score by 13. The MDS Task Force PD-MCI inclusion criteria require individuals to present with cognitive deficits that do not significantly impact upon their functional independence. Therefore, an UPDRS-II summary index score greater than three was used to exclude participants reporting significantly impaired activities of daily living.

2.2.3.10 Depression. The *Depression, Anxiety, and Stress Scale -21* (DASS-21) was used to assess presence of depression that may have impacted cognitive functioning (Lovibond & Lovibond, 1995). The DASS-21 measures depression, anxiety and stress. Participants were asked to report the degree to which they experienced a range of psychological symptoms over the past week, using a 4-point Likert scale ranging from 0 (*did not apply to me at all*) to 3 (*applied to me very much*). Example items include "*I couldn't seem to experience any positive feeling at all*" and "*I felt that I wasn't worth much as a person*" (Lovibond & Lovibond, 1995). For each dimension, scores may range from 0 to 21, with higher scores indicating greater experience of respective symptoms (e.g., depression). Henry and Crawford (2005) reported strong internal consistency ($\alpha = .88$) for the depression subscale of the DASS-21. Comorbid depression significantly impacts cognitive functioning, activities of daily living and quality of life in PD (Lawrence, Gasson, Kane, Bucks, & Loftus, 2014; Weintraub & Burn, 2011). Depression was therefore included to examine whether participants with PD-MCI reported increased depressive symptoms when compared to those with normal cognition.

2.2.4 Procedure

2.2.4.1 Ethical and clinical registration. This research was approved by Curtin University's Research Ethics Committee prior to contact with participants (approval number: HR 189/2014). This study, as part of the larger study (Chapter 4),

was registered with the Australian New Zealand Clinical Trials Registry (ACTR number: 12614001039673).

2.2.4.2 Recruitment. Participants were recruited through several avenues. Print advertisements for the study were published in the Parkinson's Western Australia (PWA) newsletter and the 'Have-A-Go' News, a community newspaper popular among older adults in the metropolitan area of Western Australia. Curtin University released a media statement targeting television networks, which led to a national news health story on the Channel Nine News Network. The news story included an interview with a participant explaining their experience in the study and an interview with the lead researcher outlining the details of the study. After this news release, the lead researcher completed a live television interview during the following morning's Channel Nine News broadcast. The study was also registered on the Michael J Fox Foundation's Fox Trial Finders website, an international registry of clinical trials being conducted in PD. Individuals self-referred and were sent an information pack (e.g., information sheet, consent form, inclusion criteria, demographic questionnaire, Curtin University map).

2.2.4.3 Neuropsychological assessment, diagnosis and subtypes. Potential participants who contacted the researcher were screened via telephone (Brandt et al., 1988), and were sent an information pack. Individuals who met inclusion criteria were scheduled for a neuropsychological assessment. Neuropsychological assessments were conducted by the primary researcher and two assistant researchers who have extensive clinical training in the delivery, scoring, and interpretation of neuropsychological tests. Each assessment took 2 to 3 hours to complete (depending on performance) and were conducted during participants' 'ON' stage of medication use. At completion of the assessment participants were reimbursed for their travel costs and thanked for their participation with a $10 gift card. Following each assessment, results were scored and interpreted using standardised normative data from healthy older adults (see Appendix B). PD-MCI was diagnosed as less than one standard deviation (SD) below normative scores on two or more neuropsychological tests (Litvan et al., 2012). The MDS Task Force suggest the use of 1 to 2 SD cut offs below normative scores. A cut off of 1 SD was used in this study to account for the likelihood that the community based cohort may include higher functioning adults

living independently, who may not report cognitive deficits but demonstrate impairment during formal neuropsychological assessment. Also, subjective report of cognitive decline has shown low accuracy in PD (Copeland, Lieberman, Oravivattanakul, & Tröster, 2016). Therefore, individuals in this study were not required to meet the criteria of reporting cognitive decline.

The following PD-MCI subtype classifications were applied: (1) amnestic single domain (impairment on two memory tests); (2) nonamnestic single domain (impairment on two or more non-memory tests); (3) amnestic multiple domain (impairment on two or more tests, including memory) and (4) nonamnestic multiple domain (impairment on two or more tests, not including memory). Raw scores were used to determine impairment on all tests, excluding the LNS and Similarities tests. The LNS and Similarities raw scores were converted into scale scores (as per WAIS-IV instructions), and then compared to normative data (Wechsler, 2008).

2.2.4.4 Data collection. Neuropsychological assessments were completed at a time convenient for each participant and data collected for this study forms part of the pre-intervention (baseline) data for Study 3 (see Chapter 4).

2.2.5 Data analysis

The Statistical Package for the Social Sciences (SPSS) 22.0 was used to complete statistical analyses. Descriptive statistics (e.g., means and SDs) for demographic data and neuropsychological test scores were computed, and frequency estimates were calculated to describe the prevalence of cognitive impairment and PD-MCI subtypes. Independent samples *t* tests and Mann-Whitney *U* tests examined outcome differences between the 'PD-MCI' and 'Normal Cognition' groups (Field, 2013; Howell, 2013). An alpha level of .05 was applied to demographic variables and a Bonferroni-adjusted alpha level for multiple comparisons was applied to cognitive outcomes per domain (i.e., $p < .025$).

2.2.5.1 Between-group comparisons. Independent samples *t* tests and Mann-Whitney *U* tests (for non-parametric outcomes) determined if there was a statistically significant difference between the 'PD-MCI' and 'Normal Cognition' groups on demographic variables and neuropsychological outcomes (Field, 2013).

2.2.5.2 Assumption testing. Two statistical assumptions pertain to independent samples *t* tests: normality and homogeneity of variance (Howell, 2013). Normality refers to the distribution of scores on outcome variables demonstrating a relatively symmetrical inverted U-shape distribution, with most participant scores grouped in the center of the distribution and less scores at either end of the distribution (Field, 2013). The normality assumption was assessed using visual inspection of histograms and Quantile-Quantile (Q-Q) Plots and the Shapiro-Wilk statistic, which is suitable for group sizes less than 50 (Tabachnick & Fidell, 2013). Homogeneity of variance assumes that each group's scores are homogeneous (equal) in their variability (Field, 2013). Levene's Test for Equality of Variances was used to examine homogeneity of variance across groups. For outcomes that violated homogeneity of variance, 'equal variances not assumed' results were reported. All assumptions (independence, scale of measurement) for Mann-Whitney *U* tests were met prior to analysis.

2.2.5.3 Internal reliability. A test's internal reliability reflects the extent to which items within a test measure one latent cognitive/psychological construct (Strauss et al., 2006). Where possible, internal reliability was computed using two methods: (1) the Kuder-Richardson 20 (KR-20) and (2) Cronbach's α (Anastasi & Urbina, 1997; Cronbach, 1951). Both methods produce estimates of internal consistency, though the KR-20 assesses tests with dichotomous response items (e.g., 'correct' or 'incorrect') and Cronbach's α examines tests with any response scale (Cortina, 1993). For cognitive tests, internal consistency of $\geq .70$ is acceptable for research purposes (Field, 2013).

2.3 Results

2.3.1 Missing data

Participants who completed neuropsychological assessments provided data for all demographic and outcome variables, excluding one participant who did not report years of disease duration. Missing values analysis was conducted and Little's Missing Completely at Random (MCAR) test showed this missing datum was not systematically linked to included variables, χ^2 (19) = 18.70, p = .48. Expectation

Maximisation (EM) was used to replace this missing value (Tabachnick & Fidell, 2013).

2.3.2 Demographic and cognitive characteristics

In total, 70 participants completed neuropsychological assessments, with 64.3% (*N* = 45) classified as PD-MCI and remaining participants classified as Normal Cognition (*N* = 25). Levodopa equivalent dose (LED) was calculated using the Tomlinson et al. (2010) method.

2.3.3 PD-MCI versus Normal Cognition results

2.3.3.1 Assumption testing. Normality was violated (Shapiro-Wilk = $p <$ .05) for several demographic and outcome variables. For the Normal Cognition group, age, premorbid IQ, disease duration, depression, SOC, Paragraph Recall, BNT, and JLO showed non-normal distributions. For the PD-MCI group, age, premorbid IQ, disease duration, depression, LED, TICS, MMSE, LNS (scale score), Paragraph Recall, BNT, Similarities (scale and raw scores), and JLO showed non-normal distributions. Visual inspection of histograms revealed negatively skewed distributions for cognitive outcomes (e.g., MMSE, BNT) and positively skewed distributions for demographic variables (e.g., disease duration, LED). However, these distributions may accurately represent this higher functioning cohort. It is possible that people with less daily LED and more years of education will have less years of disease duration (positive skewness) and likely perform within the top range of a cognitive test (negative skewness). Q-Q plots showed data to cluster relatively close to diagonal lines across all outcomes and *t* tests are robust in the face of normality violations (Tabachnick & Fidell, 2013). Therefore, no data transformation technique was applied. Between-groups homogeneity of variance was violated (Levene's test: $p < .05$) in six outcomes (MMSE, PD-CRS, LNS, BNT, JLO, and HVOT). Consequently, 'equal variances not assumed' results were reported for these outcomes. Assumption test results for all outcomes can be found in Appendix C.

2.3.3.2 Internal reliability of outcomes. Internal reliability varied between excellent (> .90) to adequate (.40 to .50) and was computed for 10 outcomes: UPDRS-II (α = .80), DASS (α = .88), TICS (KR-20 = .47), MMSE (KR-20 = .54);

PD-CRS (α = .84), LNS (KR-20 = .92), Stroop (Colour-Word) Test (KR-20 = .96), BNT (KR-20 = .54), Similarities (α = .68), JLO (KR-20 = .90) and HVLT (KR-20 = .78). Low internal reliability scores were identified for the TICS, MMSE, BNT and Similarities outcomes. However, due to the diversity of cognitive constructs, using cut off scores for Cronbach's α may subtract from the scale's primary purpose in the context of the research (Kline, 1999). All outcomes were therefore reported in this study and the current authors suggest interpreting the outcomes with low reliability with caution.

2.3.3.3 Group differences. For demographic variables and depression, independent samples *t* tests showed no statistically significant differences ($p > .05$) between the PD-MCI and Normal Cognition groups (see Table 1). However, there were significant differences between groups on all cognitive outcomes (excluding SOC). Compared to the Normal Cognition group the PD-MCI group performed worse on the TICS ($p = .004$), MMSE ($p = .001$) and PD-CRS ($p < .001$) measures of global cognition. For executive function, the PD-MCI Group performed worse on the COWAT ($p < .001$) but not SOC ($p = .76$). For attention/working memory, the PD-MCI Group performed worse on LNS (scale, $p < .001$; raw, $p = .001$) and the Stroop (Colour-Word) Test ($p < .001$). For memory, the PD-MCI group performed worse on HVLT ($p < .001$) and Paragraph Recall ($p < .001$). For language, the PD-MCI group performed worse on the BNT ($p < .001$) and Similarities (scale, $p < .001$; raw, $p < .001$). For visuospatial abilities the PD-MCI group performed worse on the JLO test ($p < .001$) and HVOT ($p < .001$).

Table 1

Comparison of demographic and neuropsychological test scores for PD-MCI and Normal Cognition groups

		PD-MCI (*N* = 45)		NC (*N* = 25)		Diff. of means	
Domain	Outcome	*M*	*SD*	*M*	*SD*	*t*	*p*
	Gender (% ♀)	62.2% (*N* = 28)		64% (*N* = 16)		–	.88[+]
	Age[++]	68.53	9.92	64.12	7.10	-1.96	.05
	Education[++]	13.60	3.10	14.52	2.87	1.22	.23
	Premorbid IQ	106.97	8.01	106.81	21.71	-.04	.97
	Disease Durat.[++]	5.81	4.58	5.90	4.99	.08	.94
	Depression	2.84	3.24	2.45	2.19	-.52	.60
	LED	398.43	350.33	335.19	254.15	-.79	.43
	UPDRS-II	1.08	0.62	0.89	.54	-1.30	.20
Global	TICS	22.42	2.95	24.48	2.47	2.96	**.004***
	MMSE	25.56	2.95	27.84	1.62	3.57[×]	**.001***
	PD-CRS	81.07	19.48	100.28	12.10	4.47[×]	**.001****
EF	COWAT	32.24	15.01	45.80	12.36	3.85	**.001****
	SOC	6.22	2.08	7.24	2.06	1.96	.60
Atten.WM	LNS (SS)	8.36	3.64	11.56	2.16	4.02	**.001****
	LNS (RS)	16.09	5.88	20.52	2.43	3.59[×]	**.001***
	Stroop Test	24.51	12.19	38.24	10.05	4.80	**.001****
Memory	HVLT	21.60	6.82	28.80	5.48	4.53	**.001****
	Para. Recall	4.56	2.31	7.08	1.79	4.71	**.001****
Language	BNT	13.27	1.66	14.32	.80	2.98[×]	**.001****
	Similarities (SS)	8.76	1.88	10.84	1.52	4.74	**.001****
	Similarities (RS)	21.09	3.97	26.40	2.75	5.93	**.001****
VS	JLO	21.29	7.62	26.64	3.49	3.31[×]	**.001***
	HVOT	22.11	3.96	25.24	2.10	4.32[×]	**.001****

Note. *M* = mean; *SD* = standard deviation; EF = executive function; Atten.WM = attention/working memory; VS = visuospatial abilities; Global = global cognition; ADL = activities of daily living; QOL = quality of life; COWAT = Controlled Oral Word Association Test; SOC = Stockings of Cambridge; LNS = Letter-Number Sequencing; HVLT = Hopkin's Verbal Learning Test; BNT = Boston Naming Test; JLO = Judgement of Line Orientation; HVOT = Hooper's Visual Orientation Test; MMSE = Mini-Mental State Examination; PD-CRS = Parkinson's Disease – Cognitive Rating Scale; UPDRS-II = Unified Parkinson's Disease Rating Scale – section II (ADL); PDQ-39 = Parkinson's Disease Questionnaire-39; SS = Scaled score; RS = Raw score; [+] = non-parametric Mann-Whitney *U* test; [++] = years; [×] = equal variances not assumed; * = $p < .05$; ** = $p < .001$.

2.3.4 PD-MCI subtypes according to MDS criteria

Most participants who met the MDS Task Force criteria for PD-MCI presented with multiple domain impairment compared to single domain (see Figure 2). Multiple domain impairment was present in 93.4% of participants, with 6.6% showing single domain impairment (4.4% memory and 2.2% visuospatial).

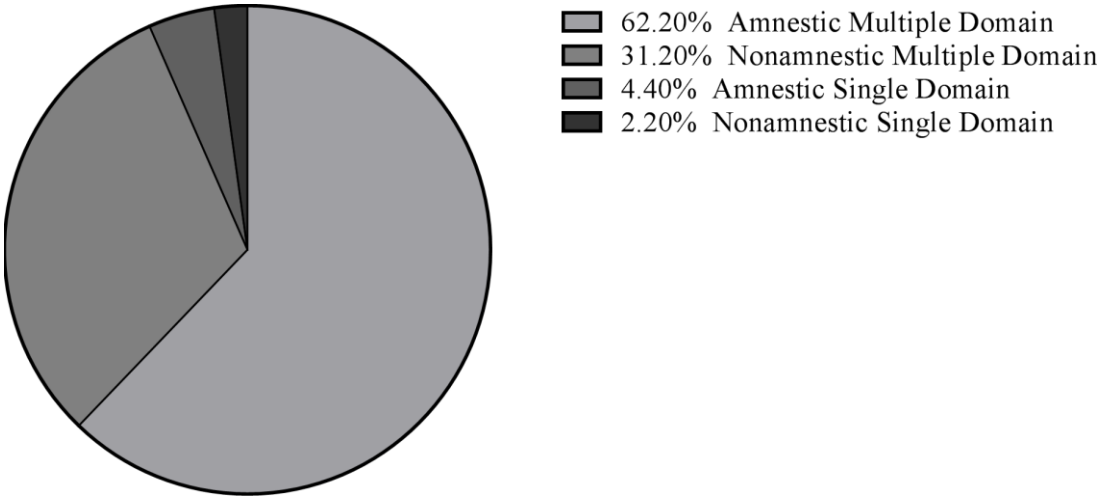

Figure 2. Distribution of PD-MCI Subtypes.

Cognitive deficits were heterogeneous among participants with multiple domain PD-MCI. In total, 62.2% (*N* = 28) of participants were classified as amnestic multiple domain with 11 different patterns of impairments identified (see Table 2). Moreover, 31.20% (*N* = 14) of participants were classified as nonamnestic multiple domain and nine sets of impairments were identified. When comparing individual cognitive domains for all PD-MCI (see Figure 3), executive function was impaired in 62.2% (*N* = 28) of participants, attention/working memory in 66.7% (*N* = 30), memory in 66.7% (*N* = 30), visuospatial in 31.2% (*N* = 14) and language in 44.4% (*N* = 20).

Table 2

Distribution of PD-MCI subtypes and domain impairments using a one standard deviation cut off score.

PD-MCI Subtype	Domains Impaired	*N* (%)
Amnestic Multiple	All domains	5 (11.1)
	Memory + EF	5 (11.1)
	Memory + Attention/WM	5 (11.1)
	Memory + EF + Attention/WM	3 (6.7)
	Memory + Attention/WM + Language	3 (6.7)
	Memory + EF + Attention/WM + Language	2 (4.4)
	Memory + EF + Attention/WM + Visuospatial	1 (2.2)
	Memory + Attention/WM + Visuospatial	1 (2.2)
	Memory + Language	1 (2.2)
	Memory + EF + Language	1 (2.2)
	Memory + Language + Visuospatial	1 (2.2)
	Subtotal	28 (62.2)
Nonamnestic Multiple	EF + Attention/WM	4 (8.8)
	EF + Language	3 (6.7)
	EF + Visuospatial	1 (2.2)
	EF + Attention/WM + Language	1 (2.2)
	EF + Attention/WM + Language + Visuospatial	1 (2.2)
	EF + Attention/WM + Visuospatial	1 (2.2)
	Attention/WM + Language	1 (2.2)
	Attention/WM + Visuospatial	1 (2.2)
	Attention/WM + Language + Visuospatial	1 (2.2)
	Subtotal	14 (31.2)
Amnestic Single	Memory	2 (4.4)
Nonamnestic Single	Visuospatial	1 (2.2)
	Total	45 (100)

Note. PD-MCI = Parkinson's Disease-Mild Cognitive Impairment; EF = executive function; Atten.WM = attention/working memory; VS = visuospatial abilities.

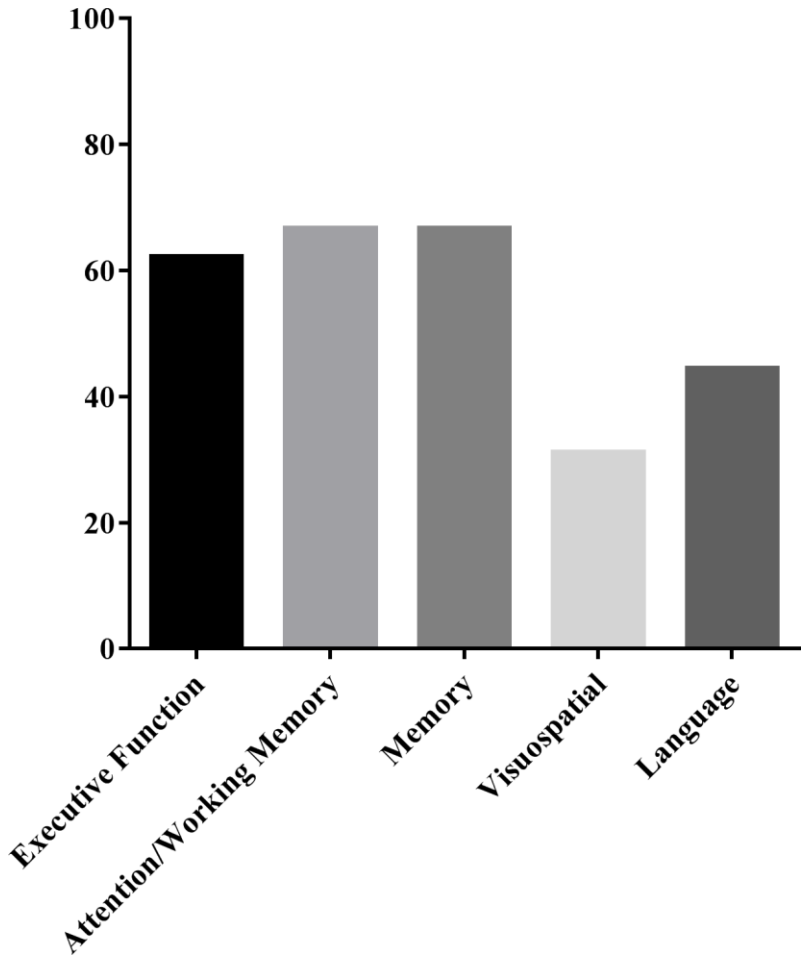

Figure 3. Percentage of Participants with Cognitive Impairment by Domain.

2.3.5 Post-hoc analyses.

Following the high frequency of PD-MCI (64.3%) when using a 1 SD cut-off below normative data, post-hoc analyses were conducted to examine whether using a 2 SD cut off would result in frequency differentials (Table 3). The frequency of PD-MCI decreased from 64.3% to 28.6% (*N* = 20). Among participants with PD-MCI, however, the frequency of subtype classifications remained relatively stable. Overall, 90% (*N* = 18) of participants with PD-MCI demonstrated multiple domain impairment and only 10% showed single domain impairment (*N* = 1 for memory and *N* = 1 for attention/working memory). Amnestic multiple domain remained most frequent (*N* = 10, 50%) with five different patterns of impairments, followed by nonamnestic multiple domain (*N* = 8, 40%) with five different patterns of impairments. Both amnestic single and nonamnestic single domains showed the least frequency of impairment (*N* = 1, 5% individually). Following the 2 SD cut off,

executive function was impaired in 75% (*N* = 15) of participants, attention/working memory in 45% (*N* = 9), memory in 50% (*N* = 10), visuospatial in 45% (*N* = 9) and language in 10% (*N* = 2).

Table 3

Distribution of PD-MCI subtypes and domain impairments using a two standard deviation cut off score.

PD-MCI Subtype	Domains Impaired	*N* (%)
Amnestic Multiple	Memory + EF	4 (20)
	Memory + EF + Attention/WM + Visuospatial	3 (15)
	Memory + EF + Attention/WM	1 (5)
	Memory + Attention/WM	1 (5)
	Memory + Language	1 (5)
	Subtotal	10 (50)
Nonamnestic Multiple	EF + Visuospatial	4 (20)
	EF + Attention/WM	1 (5)
	EF + Language	1 (5)
	EF + Attention/WM + Visuospatial	1 (5)
	Attention/WM + Visuospatial	1 (5)
	Subtotal	8 (40)
Amnestic Single	Memory	1 (5)
Nonamnestic Single	Attention/WM	1 (5)
	Total	20 (100)

Note. PD-MCI = Parkinson's Disease-Mild Cognitive Impairment; EF = executive function; Atten.WM = attention/working memory; VS = visuospatial abilities.

2.4 Discussion

2.4.1 Main findings

This study is the first application of MDS Task Force criteria for PD-MCI in an Australian sample of people with PD. In accordance with criteria, 64.3% of

participants were diagnosed as PD-MCI. Among those with PD-MCI, 93.4% presented with multiple domain impairments (i.e., deficit test results in more than one cognitive domain), and 6.6% with single domain impairment. For individual domains, attention/working memory, executive function and memory impairments were most frequently impaired. Language and visuospatial abilities demonstrated less impairment. These results are consistent with Cholerton et al. (2014) and Goldman et al. (2013) who found 63% to 67% of their samples had PD-MCI and 91.5% to 95% of those participants had multiple domain impairments. Marras et al. (2013) reported that 93% of their sample with PD-MCI had multiple domain PD-MCI, despite an overall prevalence of only 33%. Recent application of the new criteria also revealed that attention/working memory, executive function and memory domains were most frequently impaired in PD-MCI (Cholerton et al., 2014; Goldman et al., 2013). These results, however, conflict with prevalence statistics preceding the new diagnostic criteria. Earlier studies reported a significantly lower prevalence (19% to 38%) of PD-MCI, and some studies identified single domain impairment more common than multiple domain impairment (Caviness et al., 2007; Goldman, Weis, Stebbins, Bernard, & Goetz, 2012; Litvan et al., 2011).

Several reasons have been proposed for the varying frequency of PD-MCI across studies. Compared to methods used in earlier studies, the new diagnostic criteria is less stringent when diagnosing multiple domain (i.e., impairment on one test per domain) compared to single domain (i.e., impairment on two tests in one domain) subtypes, which will invariably identify more people with multiple domain impairment (Goldman et al., 2013). Introducing a more conservative criterion for the multiple domain subtype (e.g., impairment on two tests per domain) will likely reduce the biased frequency of multiple domain impairment. In addition, several verbal memory, visuospatial, and attention tests have demonstrated appropriate diagnostic specificity for PD-MCI (Biundo et al., 2013), and administering these tests in future research may provide a more accurate estimate of the multiple domain subtype.

In studies preceding the MDS Task Force criteria, variable use of SD cut offs increased the heterogeneity of the frequency of PD-MCI and this issue is yet to be resolved (Liepelt-Scarfone et al., 2011). The new diagnostic criteria suggest 1 to 2

SD cut offs when establishing cognitive impairment with normative data (Litvan et al., 2012), but Liepelt-Scarfone et al. (2011) have shown PD-MCI diagnoses vary between 56.4% (using < 1 SD) and 9.9% (using < 2 SDs). A study recently identified 2 SDs as the most sensitive and specific cut off for diagnosing PD-MCI using the new criteria (Goldman et al., 2013). Using a 2 SD cut off in the current study reduced the frequency of PD-MCI from 64.3% (using 1 SD) to 28.6%, but the frequency of subtype classifications remained relatively stable (i.e., multiple domain impairment remained more frequent than single domain). Language impairment, however, reduced from 44.4% (N = 20) using a 1 SD cut off to 10% (N = 2) using a 2 SD cut off. Compared to other cognitive domains, this result suggests that language impairment may be less frequent in PD-MCI. Impairment across all cognitive domains was prevalent among 11.1% (N = 5) of participants using a 1 SD cut off, but this reduced to nil participants using a 2 SD cut off. This finding supports the current characterisation of PD-MCI, with most individuals demonstrating impairment within multiple, but not all, cognitive domains (e.g., executive function and memory; Cholerton et al., 2014). Using a 1 SD cut off may, however, be too liberal and not sufficiently specific for identification of PD-MCI subtypes (Goldman et al., 2013). Overall, the reduction in the frequency of PD-MCI is similar to previous prevalence estimates that adopted more conservative 1.5 SD (Marras et al., 2013), and 2 SD (Muslimović et al., 2005) cut off scores. The MDS Task Force, however, suggest using a 1 SD cut off to detect impaired cognition in higher functioning individuals, who may have noticed a decline in their cognitive functioning but do not meet the stricter criteria of 1.5 to 2 SDs (Litvan et al., 2012).

The inconsistent use and weighting of cognitive tests per domain may also bias diagnosis and subtyping of PD-MCI. The MDS Task Force recommends two tests per cognitive domain to ensure consistency across studies and reliable external validity of results (Litvan et al., 2012). Recent studies adopting the criteria have used between 3 and 7 tests/subtests per domain, more than recommended (Cholerton et al., 2014; Goldman et al., 2013). Inclusion of more tests in any one domain increases the risk of a Type I error and may falsely inflate the prevalence of PD-MCI (Loftus et al., 2015). A recent study showed that when using MDS Task Force recommendations (10 or more neuropsychological tests), approximately 13% of people with PD and normal cognition will demonstrate impaired performance on two

or more tests (Loftus et al., 2015). The recent increase in prevalence of PD-MCI may, therefore, be associated with inclusion of more neuropsychological tests which may lead to more false-positive diagnoses of cognitive impairment. As previously noted, a more conservative use of tests (e.g., impairment on two tests per domain) when diagnosing multiple domain PD-MCI and applying a more stringent cut off score (e.g., < 2 SDs below normative data) may reduce the risk of Type 1 errors in research and clinical settings. While acknowledging these issues, further refinement of the PD-MCI criteria will determine the ideal classification method, appropriate cut off scores and optimal number and selection of tests for diagnosis.

Although recent studies have used variable cut off scores, subtype classifications in this study are consistent with recent findings (Geurtsen et al., 2014). Most participants were classified as multiple domain PD-MCI, which included 20 different combinations of impaired domains. Cholerton et al. (2014) also found 19 combinations of impaired domains within their multiple domain subtype. Although this may be an artefact of the diagnostic criteria (i.e., 1 SD cut off has shown low specificity; Goldman et al., 2013), this heterogeneous distribution across multiple domains is a hallmark feature of PD-MCI (Kehagia et al., 2010). Research has identified diverse pathophysiological changes and characteristics that underline the heterogeneous presentation of PD-MCI (Cosgrove et al., 2015).

Most participants in this study showed memory and executive function impairments, but there were considerable concomitant deficits across domains. The variability of PD-MCI has been associated with protein/neurotransmitter abnormalities and genetic characteristics (Cosgrove et al., 2015). Specifically, catecholaminergic changes involving frontostriatal dopaminergic deficits are associated with executive function impairment and deficiency of acetylcholine is associated with impaired posterior cortical function of memory, language and visuospatial abilities (Cosgrove et al., 2015; Svenningsson, Westman, Ballard, & Aarsland, 2012; Williams-Gray et al., 2009). In addition, alpha-synuclein infiltration (as Lewy based pathology) of the limbic system and neocortex has been associated with amnestic cognitive impairment in PD (Compta et al., 2011). Diverse neurotransmitter changes demonstrate the complex pathology of different cognitive impairments in PD.

Kehagia et al. (2010) suggest that genetic characteristics may account for patterns of decline in PD-MCI. The 'dual syndrome hypothesis' proposes two distinct genetic syndromes (executive and posterior cortical) that affect executive function and memory/visuospatial abilities in PD, and often present in early disease stages (Kehagia et al., 2010). A recent study tested the hypothesis and found associations between a genetic variation (rs4680 polymorphism of the COMT gene) which modulated executive function and two genetic variations (APOE allelic and MAPT haplotype) which independently modulated posterior cortical functions of memory and visuospatial abilities, respectively (Nombela et al., 2014). These studies provide initial support for subtyping of PD-MCI, indicating that frontal or posterior cortical deficits are associated with specific genetic and neurotransmitter abnormalities. Neuroimaging was beyond the scope of the present study, but the heterogeneity of multiple domain PD-MCI in this study does not support the 'dual syndrome hypothesis'. That being said, research shows considerable overlap between the executive and posterior cortical syndromes and further clinical trials combining neuroimaging and neuropsychological testing are required (Kehagia, Barker, & Robbins, 2013).

Participants with PD-MCI performed significantly worse (compared to participants with 'Normal Cognition'), across all cognitive domains, including measures of global cognition. Similar results were reported by Goldman et al. (2013) and Marras et al. (2013). In both of these studies, PD-MCI groups performed worse on cognitive outcomes compared to the unimpaired groups. Group allocation was determined by cognitive performance, and as such, significant differences between group scores were to be expected. However, a conflicting result was reported for executive function. Compared to the Controlled Oral Word Association Test (COWAT), scores on the Stockings of Cambridge (SOC) test demonstrated no difference between groups, indicating comparative performance between those with and without PD-MCI. A recent systematic review and meta-analysis highlighted the multifaceted nature of executive function and challenges in researching this cognitive domain in PD (Kudlicka, Clare, & Hindle, 2011). Executive function is often referred to as an 'umbrella' concept used to described many subcomponent abilities, including purposive action (execution), volition, planning, effective performance,

attentional control, set-shifting, abstract reasoning, and managing behaviour (Lezak et al., 2012; Smith & Jonides, 1999; Stuss & Alexander, 2007). Consequently, individual neuropsychological tests are often unable to capture and measure the full spectrum of executive function. Predominantly, the SOC test involves rule learning, planning and execution, whereas the COWAT requires set shifting (between trials) and attentional control. In addition, studies have shown separation of 'hot' and 'cold' executive function abilities. 'Cold' cognitive tasks are described as neutrally affective and involve cognitive flexibility, while 'hot' cognitive tasks are influenced emotion and motivated reasoning (Zelazo & Carlson, 2012). Due to the complexity of executive function and the inherent specificity of neuropsychological tests, people with PD may show impaired performance on individual tests which do not represent impairment across the entire domain (Kudlicka et al., 2011). Therefore it is important that the exact tests used for diagnosis are standardised.

When examining demographic variables, there were no significant differences between groups. Participants in the PD-MCI group were slightly older and had slightly less years of education, but differences were not significant. Recent studies have reported no educational difference between people with and without cognitive impairments in PD (Caviness et al., 2007; Cholerton et al., 2014; Goldman et al., 2013; Marras et al., 2013). But other studies reported older age and less years of education associated with cognitive decline in PD (Elgh et al., 2009; Hu et al., 2014; Williams-Gray et al., 2009). These conflicting results suggest future longitudinal research is required to determine the long-term relationship between years of education and cognitive impairment in PD. Motor symptom severity was not measured in the current study, however, other factors such as daily levodopa equivalent dose and disease duration did not differ between groups, which suggests severity of motor symptoms may have been similar across groups (Fahn et al., 2004) and no worse for participants with PD-MCI.

2.4.2 Limitations and recommendations for future research

The primary limitation of this study was the cross sectional design, involving only baseline cognitive assessments. Collecting data at one time-point limits examination of which neuropsychological tests are most appropriate and which

domains of impairment are most predictive of cognitive decline in PD. Also, this sample had relatively high educational levels and low years of disease duration. These characteristics are comparable to cohorts from recent studies (Cholerton et al., 2014; Marras et al., 2013), but may limit the generalisability of the results to the wider PD population. Some measures included in this study may have not been appropriate for detecting cognitive impairments in PD. For example, the COWAT is classified as a measure of executive function, but the timed nature of the test also requires participants' use of processing speed (Lezak et al., 2012). Processing speed is frequently impaired in PD (Litvan et al., 2011; Muslimovic et al., 2005). Participants may therefore demonstrate impaired performance on the COWAT, as a result of impaired processing speed, rather than deficits in executive function. In addition, the Similarities test was included as a measure of language abilities but it also involves higher-order cognitive skills such as, conceptualisation and abstract reasoning (Wechsler, 2008). When completing tasks involving these higher-order cognitive skills the prefrontal cortex is predominantly activated, yet people with PD are known to experience frontostriatal dopaminergic deficits, which adversely impact associated cognitive abilities (Cosgrove et al., 2015). Poor performance on the Similarities test may therefore represent impaired conceptualisation and abstract reasoning, as opposed to deficits with language abilities. Lastly, the statistical assumptions of normality and homogeneity of variance were violated for some outcomes, and there was low internal consistency for some cognitive measures. Although outcome distributions were representative of this cohort, these caveats must be noted when interpreting the results.

Future studies should adopt longitudinal designs to validate and provide suggestions for the refinement of the MDS Task Force diagnostic criteria for PD-MCI. Future studies need to determine which neuropsychological tests are most reliable and valid over time, the most appropriate number of tests per cognitive domain (to control inflation of Type I errors), tests most suitable for detecting cognitive impairment in PD (e.g., additional processing speed and language tests), and the most sensitive and specific cut off scores for diagnostic purposes. The MDS criteria also needs to be applied to different age groups with varying degrees of cognitive impairment, disease severity and cognitive reserve (educational/ occupational attainment). Recent and ongoing longitudinal studies are examining

biomarker, epidemiological and neuropsychological risk factors associated with cognitive decline in PD (Dujardin et al., 2015; Hu et al., 2014; Loftus et al., 2015; Nombela et al., 2014; Williams-Gray et al., 2009). However, future studies need to adopt an interdisciplinary approach by integrating clinical neuroscience, neuroimaging and neurobiology with the MDS criteria, to provide a greater understanding of PD-MCI. Moreover, studies must be transparent in their reporting of the normative datasets used to establish diagnoses of PD-MCI. As explained by Strauss et al. (2006), selection of appropriate normative data is equally as important as choosing a reliable and valid neuropsychological test. Using a normative dataset that is not a demographical match to a participant's characteristics is problematic, given that norm-referenced scores are directly tied to measurable consequences such as prevalence rates, diagnosis, and pharmacological/nonpharmacological interventions (Mitrushina, Boone, Razani, & Delia, 2005).

The etiology and profile of PD-MCI is heterogeneous with some people reverting back to normal cognition and many others progressing to PD-Dementia (Pedersen et al., 2013). Currently, there is no known therapeutic intervention to halt or delay cognitive decline in PD (Goldman & Weintraub, 2015). While clinical trials are examining the potential of pharmacological treatments, two recent studies found no improvements in cognition (Frakey & Friedman, 2014; Mamikonyan, Xie, Melvin, & Weintraub, 2015). This limited empirical support of pharmacological treatment has led to an increase in research assessing nonpharmacological interventions for cognition in PD (Hindle et al., 2013). Specifically, cognitive training and non-invasive brain stimulation have demonstrated improved cognition in PD (Pal, Nagy, Aschermann, Balazs, & Kovacs, 2010; París et al., 2011). However, most studies included participants without cognitive impairment and significant methodological heterogeneity has limited the reliability of results (Goldman & Weintraub, 2015). Despite current limitations, nonpharmacological interventions may be a therapeutic alternative for people with PD-MCI who are already burdened by complex polypharmacy.

2.5 Chapter Summary

When applying the MDS Task Force diagnostic criteria for PD-MCI, this study found 64% of participants (using a 1 SD cut off) were cognitively impaired (i.e., demonstrated PD-MCI), and this figure reduced to 28% with PD-MCI when using a 2 SD cut off. Despite the change in frequency of impairments, most participants with PD-MCI were classified as multiple domain subtype which is consistent with recent findings (Geurtsen et al., 2014). Although further validation and refinement of the diagnostic criteria is required, the significant prevalence and heterogeneous nature of PD-MCI is now documented in an Australian sample. Neurotransmitter abnormalities, genetic biomarkers and epidemiological risk factors are associated with cognitive deficits in PD. The limited evidence supporting pharmacological treatments for PD-MCI, indicates that future studies need to integrate the MDS criteria with randomised controlled trials of nonpharmacological interventions (e.g., cognitive training and non-invasive brain stimulation), and explore the potential beneficial effects of these therapies for people with cognitive impairment and PD. The next chapter is a review and meta-analysis of cognitive training and non-invasive brain stimulation trials for cognition in PD.

CHAPTER 3 Study 2. A Meta-analysis of Cognitive Training and Non-invasive Brain Stimulation for Cognition in Parkinson's Disease

3.1 Introduction

Whilst PD is classified as a movement disorder, up to 64% (see Chapter 2.3.2) of people with PD may experience cognitive deficits which negatively impact quality of life (Litvan et al., 2011). Whilst there is limited evidence supporting pharmacological treatment (e.g., cholinesterase inhibitors and memantine) for people with comorbid cognitive impairments and PD (Goldman & Weintraub, 2015; Wang et al., 2014), nonpharmacological interventions are being considered as potential therapeutic techniques for improving cognition (Hindle et al., 2013).

Initial research suggests that cognitive training may reduce cognitive decline for people with PD-Mild Cognitive Impairment and PD-Dementia (Burn, 2010; Kehagia et al., 2010). Studies using rTMS and tDCS have reported positive, but variable, effects on cognitive functioning in PD and there is a lack of consensus regarding administration methods for brain stimulation in PD (Benninger et al., 2010; Hindle et al., 2013). Sindhi and Leroi (2013) suggested that future research concerning cognitive training interventions for PD-MCI and PDD should be specifically adapted to the needs of the individual. People with PD often develop deficits in non-amnestic cognitive domains, such as executive functions and visuospatial abilities (Aarsland et al., 2010; Sindhi & Leroi, 2013). Any effective therapy therefore needs to target such deficits.

This chapter begins with a review of all controlled and uncontrolled trials of standard (non-specific) cognitive training, tailored (domain specific) cognitive training, repetitive transcranial magnetic stimulation (rTMS), and transcranial direct current stimulation (tDCS) for cognition in PD. This chapter concludes with a meta-analysis of all controlled trials of standard cognitive training, tailored cognitive training, and rTMS for cognition in PD. A meta-analysis uses statistical methods to pool multiple intervention trials into an individual standardised intervention effect (Borenstein, Hedges, Higgins, & Rothstein, 2011). Meta-analytic results provide a more accurate estimate of an intervention effect and allow for efficacy comparisons to determine whether there is consistency or heterogeneity across intervention outcomes (Borenstein et al., 2011). A recent meta-analysis of cognitive training in PD found cognitive training improves select cognitive domains in PD (Leung et al., 2015). However, this study is the first meta-analysis to stratify cognitive training into standard or tailored interventions and meta-analyse brain stimulation in PD. This chapter provides an accurate review of the empirical research and recommendations for future nonpharmacological interventions.

3.2 A Review of Cognitive Training and Brain Stimulation Interventions for Cognition in PD

3.2.1 Cognitive Training for Cognition in PD

As noted in Chapter 1 (section 8.3), recent clinical trials of cognitive training have demonstrated improved cognition in PD and PD-MCI (Hindle et al., 2013). For the purpose of this review, cognitive training was broadly defined as "…structured practice on tasks relevant to aspects of cognitive functioning … and tasks may be presented in various modalities, including pencil/paper or computerised versions." (Martin et al., 2011, p. 3). Standard cognitive training (not individualised) refers to a set of cognitive tasks administered to participants regardless of their individually different cognitive deficits. Tailored cognitive training (individualised) is customised to address specific cognitive deficits.

3.2.1.1 Standard Cognitive Training. Three uncontrolled trials have explored standard cognitive training in PD (Mohlman, Chazin, & Georgescu, 2011;

Sinforiani, Banchieri, Zucchella, Pacchetti, & Sandrini, 2004; Zimmermann et al., 2014). Sinforiani et al. (2004) examined the effect of standard computer-based cognitive training in people with cognitive impairments and PD. The standard cognitive training program involved the use of attention, abstract reasoning, and visuospatial abilities. Performance improved on measures of abstract reasoning, verbal fluency, and visuospatial abilities post-training and effects were maintained for six months (Sinforiani et al., 2004). Mohlman et al. (2011) assessed the feasibility and acceptance of a computer-based cognitive training program designed to train attentional abilities for people with PD. Executive functioning improved post-training, which was significantly related to the participant's subjective ratings of the training (Mohlman et al., 2011). Zimmermann et al. (2014) compared whether cognition-specific training and non-specific computer game training improved cognitive performance in PD. Although nonspecific computer-based training improved attention to a greater extent, both forms of training improved cognitive functioning (Zimmermann et al., 2014).

There have been eight controlled trials of standard cognitive training in PD (Costa et al., 2014; Edwards et al., 2013; Ell, 2013; Nombela et al., 2011; París et al., 2011; Pena et al., 2014; Petrelli et al., 2014; Pompeu et al., 2012). Nombela et al. (2011) examined whether six months of daily Sudoku puzzle training improved attention and working memory in people with cognitive impairments and PD, while neural activity was monitored by fMRI. Participants significantly improved on the Stroop test, which aligned with reduced patterns of frontal and parietal cortical activation (Nombela et al., 2011). In an RCT, París et al. (2011) examined whether standard multimedia and paper/pencil cognitive training improved cognitive functioning, quality of life, and activities of daily living in people with PD. Participants were randomised to a 'trained' or 'speech therapy' group (París et al., 2011). Compared to the control group, the trained group improved their performance across all cognitive domains (except language). However, no improvement was found on quality of life and activities of daily living measures (París et al., 2011). To examine whether standard cognitive training improved global cognition and activities of daily living in people with PD, Pompeu et al. (2012) compared Nintendo Wii-based cognitive and motor training (trained group) against balance exercise therapy (control group) in people with PD. Both groups significantly improved in global

cognition and activities of daily living, which were maintained for 60 days (Pompeu et al., 2012).

Ell (2013) compared targeted and non-targeted decision-rule training with a control group in people with PD. Trained groups completed 80 computer-based trials in which they were presented with a single stimulus and instructed to categorise the stimulus based on predetermined labels (Ell, 2013). The targeted group were presented with a stimulus relevant to the dimension and the non-targeted group were presented with both stimuli relevant and non-relevant to the dimension (Ell, 2013). Results showed that compared to the control and non-targeted groups, the targeted group improved in executive functions (Ell, 2013). In a RCT, Edwards et al. (2013) examined whether cognitive training improved speed of processing in PD. Participants completed 20 hours of computer-based cognitive training that focused on speed of processing skills. There were significant improvements in speed of processing for those with mild/moderate PD (Edwards et al., 2013). Costa et al. (2014) conducted a controlled trial of attentional shifting training for improvement of prospective memory in PD. Following 12 sessions of cognitive training, participants demonstrated improvements in event-based prospective memory and executive functions (Costa et al., 2014).

In a RCT, Petrelli et al. (2014) compared structured cognitive training (targeting specific cognitive domains) and unstructured cognitive training (random cognitive tasks) with a control group for improvements in cognition, depression, and quality of life in PD. Participants were assessed using a series of neuropsychological tests pre and post-intervention, and completed 12 sessions of cognitive training. Compared to the control and unstructured training groups, participants in the structured training group significantly improved their working memory (Petrelli et al., 2014). The structured group also significantly improved short-term memory, whereas the control group did not (Petrelli et al., 2014). The unstructured training group demonstrated improved control of attention, short and long-term memory, working memory, and executive functions (Petrelli et al., 2014). Pena et al. (2014) examined the impact of cognitive training on processing speed, verbal memory, visual memory, executive functions, and theory of mind in PD. Compared to the control group, participants in the training group demonstrated significant

improvements in processing speed, visual memory, theory of mind, and functional disability following three months of cognitive training (Pena et al., 2014).

3.2.1.2 Tailored Cognitive Training. Three uncontrolled studies have examined tailored cognitive training in PD (Disbrow et al., 2012; Milman, Atias, Weiss, Mirelman, & Hausdorff, 2014; Reuter, Mehnert, Sammer, Oechsner, & Engelhardt, 2012). Disbrow et al. (2012) conducted a computer-based cognitive training intervention to improve motor-related executive function in people with PD. Participants were divided into groups based on baseline motor-related executive function assessments and task difficulty was tailored to individual performance (Disbrow et al., 2012). Compared to the participants without motor impairment, there were significantly greater improvements in motor-related executive function for the participants with motor impairment (Disbrow et al., 2012). In a multimodal study, Reuter et al. (2012) compared three interventions for people with PD-MCI: cognitive training (Group A), cognitive training and transfer training (Group B), and cognitive training, transfer training, and motor training (Group C). Cognitive training was individually tailored based on baseline neuropsychological results and involved practicing executive function tasks (Reuter et al., 2012). Transfer training involved the practice of daily activities (e.g., prepare a meal, pay a bill) that had practical relevance to participants, and motor training was adapted from training traditionally used to enhance working memory and visuospatial abilities in children (Reuter et al., 2012). After four weeks of training, significant improvements in executive function tasks were evident for all groups. However, Group C improved significantly more than the other groups (Reuter et al., 2012). At a six month follow-up the improvements of Groups A and B were diminished, whereas improvements of Group C were maintained (Reuter et al., 2012). Milman et al. (2014) examined whether 12 weeks of in-home cognitive training improved gait, mobility (primary outcomes), and cognitive functioning (secondary outcome) in people with PD. Significant improvements were found in global cognitive scores at one and four-weeks post-training, but there were no improvements in executive function, attention, memory, and visuospatial abilities (Milman et al., 2014).

There are three published controlled trials of tailored cognitive training in PD (Cerasa et al., 2014; Naismith, Mowszowski, Diamond, & Lewis, 2013; Sammer,

Reuter, Hullmann, Kaps, & Vaitl, 2006). Sammer et al. (2006) compared the effect of tailored executive function training and standard physical therapy on cognitive performance in people with PD. Both groups demonstrated improved performance in executive functions post-training, but those who received the tailored training improved to a greater extent (Sammer et al., 2006). To accentuate the positive results of executive function training in PD, Naismith et al. (2013) conducted a tailored cognitive training program to improve memory. Cognitive training comprised of two-hour sessions twice a week and involved psychoeducation and tailored computer-based tasks (Naismith et al., 2013). Episodic memory and learning retention were significantly improved post-training (Naismith et al., 2013). Cerasa et al. (2014) examined neurofunctional correlates between trained cognitive domains and synaptic plasticity of those domains in people with PD. Participants completed 12 hours of computer-based cognitive training tailored to their pre-training cognitive impairments. Compared to the control group, participants in the training group demonstrated attentional improvements which increased neural resting state (fMRI) activity in the superior parietal and prefrontal dorsolateral cortices (Cerasa et al., 2014). Both cortices are associated with attention and executive functions, indicating that tailored cognitive training improves cognition in PD (Cerasa et al., 2014).

3.2.1.3 Summary of Cognitive Training. Most controlled and uncontrolled trials of standard and tailored cognitive training improved cognition in people with PD. Specifically, attention/working memory improved in six standard cognitive training and one tailored cognitive training study (Cerasa et al., 2014; Edwards et al., 2013; Nombela et al., 2011; París et al., 2011; Pena et al., 2014; Petrelli et al., 2014; Zimmermann et al., 2014). Significant improvements in executive functions were reported in five standard cognitive training and three tailored cognitive training studies (Costa et al., 2014; Ell, 2013; Mohlman et al., 2011; París et al., 2011; Pereira et al., 2013; Reuter et al., 2012; Sammer et al., 2006; Sinforiani et al., 2004). Visuospatial functions and memory improved in two and five studies, respectively (Costa et al., 2014; Naismith et al., 2013; París et al., 2011; Pena et al., 2014; Petrelli et al., 2014; Sinforiani et al., 2004). Despite recent studies demonstrating language impairments in PD-MCI (Cholerton et al., 2014; Goldman et al., 2013) no cognitive training study reported language improvements. Results from these studies suggest that as a nonpharmacological intervention, cognitive training may alleviate cognitive

deficits in PD. As noted by Hindle et al. (2013), however, intervention methodology has varied considerably across studies which may undermine the efficacy of these findings.

3.2.2 Brain Stimulation for Cognition

There are two main non-invasive brain stimulation procedures: repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS). rTMS employs an electromagnetic coil to excite or inhibit cortical functions (Barker et al., 1985; Guse et al., 2010). tDCS can be used to modulate neuronal activity by delivering low intensity (1 mA or 2 mA) electrical currents to a specific cortical region (Creutzfeldt et al., 1962; Nardone et al., 2012). Anodal tDCS and high frequency rTMS increase cortical excitability, whereas, cathodal tDCS and low frequency rTMS decrease cortical excitability (Nardone et al., 2012). Both rTMS and tDCS impact cortical excitability, although it is not known if one method induces greater long-term change (Nardone et al., 2012; Nitsche & Paulus, 2000; Pascual-Leone et al., 1998). The limited benefits of pharmacological treatments for people with PD and cognitive impairments has led researchers to investigate the effectiveness of rTMS and tDCS for modifying and delaying cortical degeneration in people with PD (Hindle et al., 2013; Wang et al., 2014).

3.2.2.1 Repetitive Transcranial Magnetic Stimulation. Although there is limited research examining the efficacy of brain stimulation interventions for cognitive impairments in PD, preliminary results are encouraging. Nine uncontrolled trials have examined the impact of rTMS on cognition in PD (Benninger et al., 2009; Epstein et al., 2007; Fregni et al., 2004; Furukawa, Izumi, Toyokura, & Masakado, 2009; Kimura et al., 2011; Mally & Stone, 1999; Sedláčková, Rektorová, Srovnalová, & Rektor, 2009; Srovnalova, Marecek, Kubikova, & Rektorova, 2012; Srovnalova, Marecek, & Rektorova, 2011).

In a preliminary study, Mally and Stone (1999) administered rTMS (1 Hz) over the skull's vertex once or twice a day to people with PD. Motor and short-term memory assessments were completed at baseline and three, seven, 30, and 90 days following stimulation (Mally & Stone, 1999). There were no improvements in short-

term memory. Fregni et al. (2004) compared rTMS and antidepressant medication (fluoxetine) on cognitive function in PD. Participants were randomised to either receiving rTMS (15 Hz) over their left dorsolateral prefrontal cortex and a placebo drug, or sham rTMS and fluoxetine (20mg; Fregni et al., 2004). Although depression was the primary outcome of this study, significant improvement in global cognition (measured by MMSE) was reported for both the rTMS and fluoxetine groups at 2-weeks post-intervention. In an open study, Epstein et al. (2007) examined the impact of rTMS on global cognition, attention, and memory in PD. Participants completed 10 sessions of rTMS (10 Hz) applied over their left dorsolateral prefrontal cortex. Global cognition and memory improved at two-weeks post-intervention. But improvements were not maintained at the three and six week follow-up assessments (Epstein et al., 2007). Sedláčková et al. (2009) investigated whether one session of rTMS (10 Hz) applied over the left dorsal premotor cortex and/or left dorsal lateral prefrontal cortex affected reaction time and executive functions in people with PD. The results did not indicate any improvements related to rTMS (Sedláčková et al., 2009).

As previous studies used 25 Hz rTMS or less, Benninger et al. (2009) investigated whether rTMS (50 Hz) could be safely delivered to people with PD and whether increased rTMS frequency would lead to improvements in cognitive and motor functions. Participants received one session of rTMS over the left primary motor cortex. Significant improvements were found in right and left-hand movements, but participants demonstrated no improvements in cognition (Benninger et al., 2009). Comparatively, Furukawa et al. (2009) examined whether low frequency rTMS (0.2 Hz) improved working memory and executive functions in PD. Six participants completed 12 stimulation sessions over 12 weeks. Significant improvements were reported for working memory and executive functions (Furukawa et al., 2009).

Srovnalova et al. (2011) examined whether rTMS over the inferior frontal gyrus improved executive functions in PD without cognitive impairment. Participants completed one active and one sham rTMS (25 Hz) session, and performed the Stroop test and Frontal Assessment Battery (FAB) prior to and immediately following each session (Srovnalova et al., 2011). Stroop test

performance improved, but FAB performance did not (Srovnalova et al., 2011). In a eight-week cross-over study of sham rTMS followed by real rTMS, Kimura et al. (2011) examined the impact of 0.2 Hz stimulation on motor symptoms, activities of daily living, depression, cerebral blood flow, and cognition in PD. Post-rTMS, only motor symptom improvements were found (Kimura et al., 2011). Another study by Srovnalova et al. (2012) compared rTMS (25 Hz) applied over either the left or right dorsolateral prefrontal cortices to examine its impact on an executive function task (Tower of London). Participants demonstrated improvements in Tower of London problem-solving time when rTMS was applied over the right, but not the left, dorsolateral prefrontal cortex (Srovnalova et al., 2012).

There are four published controlled trials of rTMS for cognition in PD (Benninger et al., 2011; Benninger et al., 2012; Boggio et al., 2005; Pal et al., 2010). Similar to Fregni et al.'s (2004) uncontrolled trial, Boggio et al. (2005) compared the effects of rTMS (15 Hz) over the left dorsal lateral prefrontal cortex or antidepressant medication (fluoxetine) on cognitive function in PD. Both interventions led to improvements in executive functions and visuospatial abilities post-treatment, which were maintained for eight weeks (Boggio et al., 2005). Pal et al. (2010) compared the effect of rTMS (5 Hz) over the left dorsal lateral prefrontal cortex and sham rTMS in PD and comorbid depression. After 10 sessions of rTMS, Stroop performance significantly improved and these improvements were maintained for 30 days (Pal et al., 2010). Although depression was the primary outcome in these studies, high frequency rTMS over the left dorsal lateral prefrontal cortex improved executive and visuospatial functions in people with PD (Boggio et al., 2005; Pal et al., 2010).

To examine the safety and efficacy of intermittent theta-burst (iTBS) rTMS, Benninger et al. (2011) conducted a RCT of eight 5 Hz sessions over two weeks. Participants received bilateral iTBS-rTMS to the primary motor and dorsolateral prefrontal cortices. Results showed decreased verbal fluency for the iTBS-rTMS group (compared to control), but no significant differences were found for executive functions (as measured by the Frontal Assessment Battery). Furthering these results, Benninger et al. (2012) conducted another RCT to examine the safety and efficacy of rTMS (50 Hz) for improving motor symptoms in PD. Executive function (FAB) was

included as a secondary outcome, but no improvements were reported (Benninger et al., 2012).

3.2.2.2 Transcranial Direct Current Stimulation. Two uncontrolled trials (Boggio et al., 2006; Pereira et al., 2013) and one controlled trial (Doruk, Gray, Bravo, Pascual-Leone, & Fregni, 2014) have examined the impact of tDCS on cognition in PD. Boggio et al. (2006) tested whether tDCS over the left dorsal lateral prefrontal cortex (DLPFC) improved working memory performance (three-back letter paradigm) in PD. Participants were assigned to one of three tDCS conditions; (i) stimulation of the left DLPFC, (ii) stimulation of the primary motor cortex, and (iii) sham tDCS. Participants were then allocated to one of two tDCS intensity groups, 1 mA or 2 mA (Boggio et al., 2006). Two mA tDCS over the left DLPFC improved working memory, whereas 1mA and sham tDCS did not improve working memory. Pereira et al. (2013) examined whether 20 minutes of counterbalanced 2 mA tDCS over the left dorsolateral prefrontal and left temporo-parietal cortices improved executive functions (phonemic and semantic fluency) in PD. Significant improvements were found in executive functions immediately following tDCS. In the only randomised controlled trial of tDCS in PD, Doruk et al. (2014) compared 2 mA tDCS applied over the left (group one) or right (group two) dorsolateral prefrontal cortex with sham stimulation (control group) for executive function in PD. Compared to the control group, significant improvements in the Trail Making Test (Part B) were found for both tDCS groups immediately following the two-week intervention and at a one-month follow-up assessment (Doruk et al., 2014).

3.2.2.3 Summary of Brain Stimulation. Most brain stimulation interventions improved cognitive functioning in PD. Attention/working memory improved in one rTMS and one tDCS study (Boggio et al., 2006; Furukawa et al., 2009). Executive function improvement was found in five rTMS and two tDCS studies (Boggio et al., 2005; Disbrow et al., 2012; Doruk et al., 2014; Furukawa et al., 2009; Pal et al., 2010; Srovnalova et al., 2012; Srovnalova et al., 2011). Improvements were also found in memory (Epstein et al., 2007) and visuospatial functions (Boggio et al., 2005). No brain stimulation study measured language

improvements. These studies provide preliminary evidence in support of non-invasive brain stimulation for improving cognitive function in PD.

3.2.3 Summary of Previous Research

Hindle and colleagues (2013) conducted a systematic review examining nonpharmacological enhancement of cognitive functions in PD. They concluded that although a large number of studies demonstrated improvements in cognitive function (predominantly executive functions) for people with PD and PD-MCI, there was a lack of methodological rigour which reduced the quality of the results (Hindle et al., 2013). rTMS studies have varied by intervention length (1 to 12 sessions), stimulation frequency (0.2 Hz to 50 Hz), target locations (dorsolateral prefrontal or motor cortices) and approach to stimulation: intermittent theta-burst or repetitive TMS (Benninger et al., 2011; Benninger et al., 2012; Benninger et al., 2009; Boggio et al., 2005; Epstein et al., 2007; Furukawa et al., 2009). Consequently, studies administering lower frequency (e.g., 5 Hz) rTMS over the left dorsolateral prefrontal cortex (impacting executive function) will likely produce different cortical effects compared to higher frequency (e.g., 50 Hz) rTMS over the motor cortices (impacting motor function). Most studies have also assessed cognitive domains as secondary outcomes, rather than targeting interventions to the primary improvement of cognition (Boggio et al., 2005; Fregni et al., 2004). For tDCS, more consistent methodology has been adopted (e.g., 2 mA stimulation of prefrontal cortices) but findings are limited by lack of controlled designs (Boggio et al., 2006; Pereira et al., 2013). The methodological differences across studies indicates a need to meta-analyse results to provide a more accurate estimate of an overall intervention effect.

Recent, controlled trials have adopted more stringent methodological designs and support cognitive training and brain stimulation for improved cognition in PD (Doruk et al., 2014; Petrelli et al., 2014). In addition, a recent meta-analysis of cognitive training in PD found improvements in working memory, processing speed and executive function (Leung et al., 2015). It remains unclear, however, whether standard or tailored cognitive training, rTMS, or tDCS are beneficial for cognition in PD. The present study builds upon the recent meta-analysis by examining the efficacy of controlled, standard cognitive training, tailored cognitive training, tDCS,

and rTMS studies in PD and provides a synthesis of current results with recommendations for future, nonpharmacological interventions.

3.3 A Meta-Analysis of Controlled Nonpharmacological Interventions for Cognition in PD

This meta-analysis systematically examines the efficacy of standard cognitive training, tailored cognitive training, tDCS, and rTMS studies for improving cognition in PD and provides a synthesis of current results with recommendations for future nonpharmacological interventions in PD. This meta-analysis was conducted in accord with the Preferred Reporting of Systematic Reviews and Meta-Analyses (PRISMA) statement (Moher, Liberati, Tetzlaff, & Altman, 2009).

3.4 Search Strategy

An extensive literature search revealed intervention studies for cognition in PD. The following key words *attention, brain, brain stimulation, cognition, cognitive, cognitive impairment, cognitive rehabilitation, cognitive therapy, cognitive training, cerebral cortex, cortex, current, direct, dorsal, dorsolateral, dorsolateral prefrontal cortex, electric stimulation, episodic memory, executive, executive function, explicit memory, function, implicit memory, intervention, language, language tests, learning, long-term memory, magnetic, memory, mild cognitive impairment, motor cortex, neuronal plasticity, neuropsychological, noninvasive, parietal lobe, Parkinson disease, prefrontal, prefrontal cortex, premotor, psychomotor, performance, rehabilitation, semantic memory, short-term memory, spatial memory, stimulation, tests, therapy, training, transcranial, transcranial direct current stimulation, transcranial magnetic stimulation, verbal memory, visual perception, visuospatial, visuospatial ability, visuospatial memory,* and *working memory* were systematically searched in online databases for published studies (Medline, PubMed, Proquest, ScienceDirect, PsycInfo, Web of Science, Wiley Online Library, EMBASE, and Cochrane Library) and grey literature (OpenGey and NTIS). Search parameters were from first date of publication to May 27, 2016. Reference lists of selected articles were also searched.

3.5 Study Selection

Studies were included in the meta-analysis if they:

1. Included participants with idiopathic PD diagnosed by a neurologist or geriatrician in accord with the United Kingdom's Parkinson's Disease Society Brain Bank Clinical Criteria (UKPDSBBC).
2. Evaluated repetitive transcranial magnetic stimulation, transcranial direct current stimulation, or cognitive training interventions in PD.
3. Used a controlled design.
4. Measured primary outcomes with standardised neuropsychological tests.
5. Provided data to calculate an effect size (means, SDs, *t* or *F* values, and probability values).

The primary researcher (B.J.L) systematically screened article titles and abstracts in-line with selection criteria, and identified preliminary articles for inclusion. The primary researcher (B.J.L) and supervisory researcher (A.M.L) then independently screened selected articles to determine the final studies for inclusion. Any disagreements were resolved through discussion.

3.6 Statistical Analysis

Comprehensive Meta-Analysis (CMA) version 3.3.070 was used to complete data analyses in accordance with recommendations by Borenstein et al. (2011), Hedges and Olkin (1985), Ray and Shadish (1996), and DerSimonian and Kacker (2007).

3.6.1 Effect Size Calculation

Hedge's g was used to represent the effect size for each study (Hedges & Olkin, 1985). Hedge's g removes the overestimate effect size bias of Cohen's d by applying the correction factor (J). Cohen's d is the standardised mean difference between control and intervention groups at post-intervention (Cohen, 1992) and was calculated before applying J to compute g (Borenstein et al., 2011). When a study reported sufficient data (pre and post-intervention means and standard deviations

[SDs] for intervention and control groups), effect sizes were calculated using change scores with the following formula:

$$d = \frac{M_{I\Delta} - M_{C\Delta}}{SD_{pooled}}$$

where: $M_{I\Delta}$ = mean change in intervention group from pre-intervention to post-intervention

$M_{C\Delta}$ = mean change in control group from pre-intervention to post-intervention

and $$SD_{pooled} = \sqrt{\frac{(n_I - 1)(\sigma_I)^2 + (n_C - 1)(\sigma_C)^2}{n_I + n_C - 2}}$$

where: n_I = number of participants (intervention group)

n_C = number of participants (control group)

σ_I = standard deviation (intervention group)

σ_C = standard deviation (control group)

Rather than computing pooled effect sizes with post-intervention means and SDs, the change score method provides a more precise estimate of an 'intervention vs. control' effect by accounting for pre-intervention group differences. Change scores ensure the within-groups absolute magnitude of change is used to calculate pooled effect sizes in a meta-analysis. Leung et al. (2015) recently used the change score method.

In some studies, underlying population standard deviations are the same across groups. However, in this meta-analysis it was unlikely that, $\sigma_I = \sigma_C = \sigma$. Therefore within-groups standard deviations were pooled across groups to provide a more accurate estimate of their combined value (Borenstein et al., 2011). For studies that reported Cohen's d, variance of d (V_d) was computed using the following formula:

$$V_d = \frac{n_I + n_C}{n_I \times n_C} + \frac{d^2}{2(n_I + n_C)}$$

(Hedges & Olkin, 1985)

Then, each study's Cohen's d was converted to Hedge's g using the below correction factor (J) formula:

$$J = 1 - \frac{3}{4df - 1}$$

Then, $$g = J \times d$$

and $$V_g = J^2 \times V_d$$

with $$SE_g = \sqrt{V_g}$$

where: $df = (n_I + n_C) - 2$

SE_g = Standard Error of g

V_g = Variance of g

(Borenstein et al., 2011; Hedges & Olkin, 1985)

When studies did not report means, standard deviations, *t* or *F* statistics, effect sizes were calculated using probability levels from a one-way two-group test (ANOVA or ANCOVA) based on post-intervention scores (Ray & Shadish, 1996). Corresponding *t*-values for reported probability levels were computed using CMA and substituted into the below formula to calculate an estimate of Hedge's g:

$$g = J \times d$$

where: $$d = \frac{t}{\left(\sqrt{Harmonic\ N\ /\ \sqrt{2}}\right)}$$

and $$Harmonic\ N = \frac{(2 \times n_I \times n_C)}{(n_I + n_C)}$$

producing: $$g = J \times \frac{t}{\left[\sqrt{\frac{(2 \times n_I \times n_C)}{(n_I + n_C)}} / \sqrt{2}\right]}$$

(Borenstein, Hedges, Higgins, & Rothstein, 2014)

Where studies reported adjusted means and standard error (SE) values at pre and post-intervention, standard error values were converted into standard deviations (SD) using the following formula:

$$SD = SE \times \sqrt{n}$$

(Altman & Bland, 2005)

3.6.1.1 Multiple outcomes per study. Studies often report multiple outcomes that are conceptually related and measure an overarching domain (e.g., memory, executive function). Selecting individual outcomes from each study to pool effect sizes may induce a selection bias towards statistically significant results or the most frequently used outcomes across studies. Borenstein et al. (2011) therefore recommend including all outcomes from all studies, by first computing composite domain effects within studies and then using the composite domain effects to pool effect sizes across studies. However, including multiple outcomes from each study within each pooled effect will produce (often high) intercorrelations between the conceptually related outcomes (Olkin & Gleser, 2009). High correlations will lead to less precise estimates of the pooled effects (Borenstein et al., 2011). Thus to account for intercorrelations between conceptually related outcomes, composite domain effects were calculated by computing the mean effect and variance within each domain within each study, and adjusting the mean variance by a factor of .80 using the below formula:

$$V_{\bar{Y}} = \frac{1}{m} V\,(1 + (m-1)\,r)$$

where: V = mean variance

m = number of conceptually related outcomes

r = correlation factor

(Borenstein et al., 2011; Leung et al., 2015)

3.6.1.2 Multiple treatment conditions. To ensure even distribution of participants, studies including two or more intervention groups and one control group had participants in the control group divided into multiple sub-control groups. This ensured that each participant's data was included only once in the meta-analysis (Borenstein et al., 2011).

3.6.2 Pooled Effect Size Calculation

There are two dominant statistical models for pooling effect sizes in a meta-analysis: a fixed-effect model and a random-effects model (Borenstein et al., 2011). The fixed-effect model assumes one true effect size among included studies and any study effect differences are due to sampling error (Borenstein et al., 2011). However, it is unlikely that all studies in a meta-analysis produce the same effect. Most studies pooled using meta-analytic techniques differ in various ways (e.g., research design, participant demographics, type and length of intervention) and despite examining the same phenomenon, this heterogeneity produces varying effects (Borenstein et al., 2011). Nonetheless, as long as studies included in a meta-analysis demonstrate a degree of similarity and combining their results will provide a valuable synthesis of information, the random-effects model accounts for differences across study effect sizes using the Hedges and Vevea (1998) 'weighting by inverse variance' method. Although less powerful than a fixed-effect model, a random effects model applies a weight to each study using both within and between-study variance to ensure that the weight (small or large *N*s) of an individual study does not over influence the pooled effect (Borenstein, Hedges, Higgins, & Rothstein, 2010). For this meta-analysis, pooled effect sizes were calculated using a random-effects model (Borenstein et al., 2010).

3.6.2.1 Within-study variance. Within-study variance (v_i) was calculated using the same formula as previously described for effect size variance:

$$v_i = \frac{n_I + n_C}{n_I \times n_C} + \frac{d^2}{2(n_I + n_C)}$$

where: n_I = number of participants (intervention group)

n_C = number of participants (control group)

d = effect size

(Hedges & Olkin, 1985)

3.6.2.2 Between-study variance. The general method-of-moments estimate was used to calculate between-study variance (T^2):

$$T^2 = \frac{Q - df}{C}$$

with: $Q = \sum \frac{(d - \bar{d})^2}{v_i}$ $df = n - 1$ $C = \sum \frac{1}{v_i} - \frac{\sum\left(\frac{1}{v_i}\right)^2}{\sum \frac{1}{v_i}}$

producing: $$T^2 = \frac{\sum \frac{(d - \bar{d})^2}{v_i} - (n-1)}{\sum \frac{1}{v_i} - \frac{\sum\left(\frac{1}{v_i}\right)^2}{\sum \frac{1}{v_i}}}$$

(DerSimonian & Laird, 1986)

Where d = effect size, $\bar{d}$ = mean effect size, n = number of studies and v_i = within-study variance. Where the value of T^2 was negative, T^2 was set to zero as variance cannot be negative (Borenstein et al., 2011).

3.6.2.3 Weighted effect size. Each outcome effect size was weighted by the inverse of its within and between-study variance. The formula below was used to assign weights to individual effect sizes:

$$W_i = \frac{1}{v_i + T^2}$$

(Hedges, 1983)

3.6.2.4 Pooled effect size. After computing weighted effect sizes for each outcome, weighted mean effect sizes were calculated to produce pooled effect sizes (M_W) for each intervention modality (rTMS, standard cognitive training, and tailored cognitive training). The below formula was used:

$$M_W = \frac{\sum W_i Y_i}{\sum W_i}$$

(Hedges, 1983)

3.6.2.5 Statistical significance. In accord with recommendations from Borenstein et al. (2011) 95% confidence intervals were calculated to test the statistical significance of each pooled effect size. The pooled effect size and standard error of the pooled effect size was used in the formula:

$$Lower\ Limit = M_W - 1.96 \times SE_{M_W}$$
$$Upper\ Limit = M_W + 1.96 \times SE_{M_W}$$

with: $SE_{M_W} = \sqrt{V_{M_W}}$ and: $V_{M_W} = \frac{1}{\sum W_i}$

producing: $Lower/Upper\ Limit = M_W \pm 1.96 \times \sqrt{\frac{1}{\sum W_i}}$

where: M_W = pooled effect size

SE_{M_W} = standard error of the pooled effect size

V_{M_W} = variances of the pooled effect size

3.6.3 Publication Bias

Publication bias occurs when researchers selectively publish significant results that support a priori hypotheses and neglect to report non-significant or

contradictory results (Rosenthal, 1979). Scientific journals often favour statistically significant and/or large effect results and this bias can influence a researcher's decision to report their results (Easterbrook, Gopalan, Berlin, & Matthews, 1991). Unfortunately, researchers often selectively report their findings (omitting non-significant or small effect sizes) and may change what they declare as *a priori* hypotheses (Chan, Hróbjartsson, Haahr, Gøtzsche, & Altman, 2004). Publication bias often results in a large amount of grey literature (unpublished results), which is challenging for the meta-analyst to source and therefore provide a more accurate synthesis of all existing scientific evidence (Borenstein et al., 2010). A meta-analysis based on published and statistically significant results has the potential to produce a pooled effect size, which may overestimate the true effect (Thornton & Lee, 2000).

In this meta-analysis, funnel plots, Egger's (1997) regression asymmetry test, and R. Rosenthal's (1979) Fail-Safe $\mathcal{N}$ method assessed publication bias. Funnel plots are a scatter plot estimate of a study's effect size (on the x-axis) against a measure of study size (usually the standard error of effect size on the y-axis) with larger sample sizes providing greater precision of intervention effect estimates (Sterne, Egger, & Smith, 2001). Therefore, a funnel plot without bias should resemble a symmetrical inverted funnel shape with small studies scattered more widely at the bottom and larger studies gathered closer together at the top (Sterne et al., 2001). The presence of publication bias is shown by an asymmetrical distribution indicating a bias towards a particular result irrespective of study size or precision. Egger's (1997) test of regression asymmetry uses a simple linear regression between the funnel plot effect sizes (x-axis) and their standard errors (y-axis), with a statistically significant result indicating the meta-analysis is impacted by publication bias.

R. Rosenthal's (1979) Fail-Safe $\mathcal{N}$ method was also used to examine publication bias. Described as the *File Drawer Problem*, Rosenthal (1979) stated that published studies are the Type 1 errors and only represent 5% of all studies conducted, while 95% of all research is left in 'file drawers' as unpublished due to non-significant results. Fail-Safe $\mathcal{N}$ refers to the number of unpublished studies

needed to reduce the significance of a meta-analytic pooled-effect size to non-significant. This formula was used to calculate Rosenthal's (1979) Fail-Safe $\mathcal{N}$:

$$Fail - safe\ N = \left[\frac{k}{{Z_C}^2}\right] \times [k\,(\overline{Z_k})^2 - {Z_C}^2]$$

where: k = number of studies

Z_C = critical Z value

$\overline{Z_k}$ = mean Z for K studies

Rosenthal (1979) asserts that a Fail-Safe $\mathcal{N}$ value greater than 5*k* +10 indicates a low likelihood of publication bias within a meta-analysis.

3.6.4 Heterogeneity Analysis

Heterogeneity of intervention effects in a meta-analysis suggests that individual interventions produce different effects across studies (Higgins, Thompson, Deeks, & Altman, 2003). A large degree of heterogeneity limits external validity and generalisability of pooled effect sizes (Higgins et al., 2003). Heterogeneity was explored using Cochrane's Q and I^2 statistics. In a meta-analysis a statistically significant Q statistic suggests a difference between an observed and true effect (Huedo-Medina, Sánchez-Meca, Marín-Martínez, & Botella, 2006). However, the Q statistic may overestimate this difference in small sample sizes. Therefore, if Q was significant the I^2 statistic, which is an estimate of the total proportion of variance in the pooled effect size, was used to examine heterogeneity between studies. Values for I^2 are expressed as a percentage with suggested values of 25% (low), 50% (moderate), and 75% (high) used to categorise levels of heterogeneity (Huedo-Medina et al., 2006). The I^2 statistic was calculated using the following formula:

$$I^2 = 100\% \times \frac{Q - df}{Q}$$

with: Q = Cochran's heterogeneity statistic

$$= \sum W_i \left(d - \bar{d}\right)^2$$

giving: $$I^2 = 100\% \times \frac{[\sum W_i (d - \bar{d})^2] - df}{\sum W_i (d - \bar{d})^2}$$

3.6.5 Meta-Regression Analysis

Meta-regression assesses whether moderator variables explain variance in heterogeneity of pooled effect size estimates (Borenstein et al., 2010). Similar to multiple regression at the participant level, where independent or covariate variables are used to predict variance in dependent variables, meta-regression uses covariate variables at the study level and dependent variables are pooled effect sizes (Borenstein et al., 2010). As with meta-analysis, there are fixed-effect and random-effects models for meta-regression. This meta-regression adopted a random-effects model with unrestricted maximum-likelihood analysis (UML) and CMA was used to conduct each meta-regression. A Z-test determines the statistical significance of the relationship between moderator variables and pooled effect sizes (Borenstein et al., 2010). Statistical significance is defined as Z-values beyond +1.96 to -1.96 limits and is calculated using this equation:

$$Z = \frac{B}{SE_B}$$

where: B = unstandardised regression coefficient

SE_B = standard error of B

3.6.6 Risk of Bias Assessment

The Cochrane Collaboration tool was used to assess risk of bias among studies included in this meta-analysis (Higgins & Green, 2008). The risk of bias assessment tool classifies individual studies as having low, high, or unclear risk of bias across six domains; sequence generation, allocation concealment, blinding, selective reporting, and other biases (Higgins & Green, 2008).

3.6.7 Data Extraction

The data extracted from each study included participants, interventions, comparisons, outcomes, and study design (PICOS). Cognitive outcomes were categorised in accordance with the Movement Disorder Society (MDS) Task Force recommendations for cognitive domains: executive function, attention/working memory, memory, visuospatial abilities, language and global cognition (Litvan et al., 2012). The MDS Task Force does not describe attention, processing speed, and working memory as individual domains. Outcomes assessing these cognitive abilities were therefore categorised within the single 'attention/working memory' domain, in accord with MDS recommendations.

3.7 Results

3.7.1 Search Results

In total, 13,162 titles and abstracts were systematically screened in online databases. Seventy one studies examined nonpharmacological interventions in PD. Fifty seven were excluded as they were not rTMS, tDCS, or cognitive training interventions (13), multiple interventions (e.g., cognitive training combined with physical exercise) (4), study protocols (3), case studies (2), not assessing cognition with standardised measures (9), not all participants diagnosed with PD (1), provided insufficient data to be meta-analysed (e.g., conference abstracts and authors did not respond to a follow up contact) (6), or not controlled trials (17). Two additional studies were excluded as the researcher was unsuccessful in obtaining missing data from the authors. Boggio et al. (2005) were contacted to provide control group means and standard deviations at Week 2. Doruk et al. (2014) were contacted to provide raw means and standard deviations. The authors did not respond and the studies were excluded. Therefore, tDCS was not included in this meta-analysis due to only one controlled trial being published and necessary data not provided (see Figure 4).

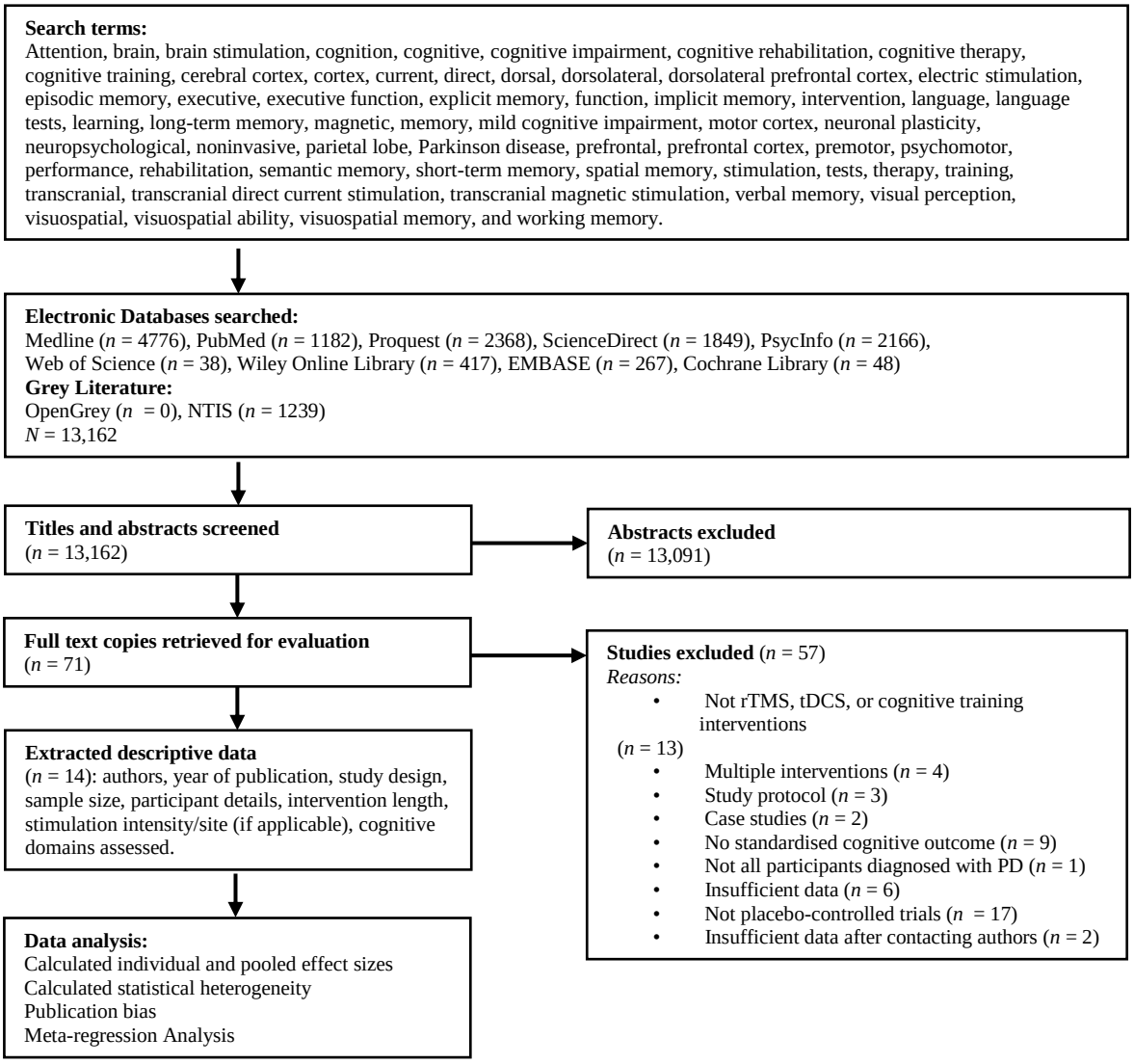

Figure 4. PRISMA Flow Chart of Search Results

3.7.2 Study Characteristics

Fourteen controlled trials met inclusion criteria (see Table 4). There were 3 rTMS (Benninger et al., 2011; Benninger et al., 2012; Pal et al., 2010), 3 tailored cognitive training (Cerasa et al., 2014; Naismith et al., 2013; Sammer et al., 2006), and 8 standard cognitive training studies (Costa et al., 2014; Edwards et al., 2013; Ell, 2013; Nombela et al., 2011; París et al., 2011; Pena et al., 2014; Petrelli et al., 2014; Pompeu et al., 2012). Publication dates ranged from 2006 to 2014, with all but one published in the past five years. For the purpose of this meta-analysis, Petrelli et al. (2014) was split into two studies, as the study compared two intervention groups against a control group. Throughout this chapter, Petrelli et al. (2014) will be referred to as two studies and referenced once.

Table 4

Participant Characteristics of all Controlled Trials included in Meta-Analysis

Intervention	Author (Year)	*N*	Age (*M*)	Male (%)	Duration of Illness (Yrs)	Education (Yrs)
rTMS	Pal (2010)	22	68	50	6.25	—
	Benninger (2011)	26	63.85	69	8.65	—
	Benninger (2012)	26	64.1	77	8.95	—
Standard CT	Nombela (2011)	20	60.65	50	8.10	7.60
	Paris (2011)	28	65.09	53.80	7.60	9.69
	Pompeu (2012)	32	67.40	53.13	—	—
	Ell (2013)*	36	66.13	—	4.70	16.33
	Edwards (2013)	73	68.78	62.07	6.94	15.15
	Costa (2014)	17	68.50	—	9.10	10.90
	Petrelli (2014)	65	69.05	43.08	5.63	13.17
	Pena (2014)	44	67.84	61.36	6.50	10.40
Tailored CT	Sammer (2006)	26	69.65	—	—	—
	Naismith (2013)	50	66.70	70.50	7.05	14.45
	Cerasa (2014)	15	59.70	—	3.35	8
	M	34	66.10	58.99	6.90	11.74

Note. *M* = mean; Yrs = years; CT = cognitive training; * = only participants with PD.

Table 5

Characteristics of all Controlled Trials included in Meta-Analysis

Intervention	Author (Year)	Cognitive Status	CT Type	CT Method	CG	No. of Sess.	Length (Hrs)	Stimul. Intensity /Site
rTMS	Pal (2010)	No CI	n.a	n.a	SH	10	.30	5Hz / Left DLPFC
	Benninger (2011)	n.a	n.a	n.a	SH	8	.08	50Hz / M1 & DLPFC
	Benninger (2012)	n.a	n.a	n.a	SH	8	.08	50Hz / M1
Standard CT	Nombela (2011)	CI	P/P	I	Act.	182	45.63	n.a
	Paris (2011)	CI (50%)	Comp. & P/P	I	Act.	12	9	n.a
	Pompeu (2012)	No CI	Comp.	I	Act.	14	7	n.a
	Ell (2013)	No CI	Comp.	I	Act.	1	.13	n.a
	Edwards (2013)	No CI	Comp.	I	W	20	20	n.a
	Costa (2014)	CI	Comp.	I	Act.	12	9	n.a
	Petrelli (2014)	No CI	Comp.	I & G	Act.	12	18	n.a
	Pena (2014)	No CI	Comp.	G	Act.	36	36	n.a
								n.a
Tailored CT	Sammer (2006)	No CI	P/P	I	Act.	10	5	n.a
	Naismith (2013)	No CI	Comp. & P/P	G	W	14	14	n.a
	Cerasa (2014)	No CI	Comp.	I	Act.	12	12	n.a
	M	n.a	n.a	n.a	n.a	25.10	12.59	n.a

Note. CT = cognitive training; CG = control group; Sess. = sessions; Stimul. = stimulation; Hz = hertz; M1 = primary motor cortex; DLPFC = dorsal lateral prefrontal cortex; CI = cognitive impairment; Comp. = computerised training; P/P = paper and pencil tasks; I = individual; G = group; SH = sham control group; W = waitlist control group; Act. = active control group.

3.7.3 Assessment of Risk of Bias

Two studies had low risk of bias (Pena et al., 2014; Petrelli et al., 2014), 5 had high risk of bias (Costa et al., 2014; Edwards et al., 2013; Naismith et al., 2013; Nombela et al., 2011; Sammer et al., 2006), and 7 had unclear risk of bias (Benninger et al., 2011; Benninger et al., 2012; Cerasa et al., 2014; Ell, 2013; Pal et al., 2010; París et al., 2011; Pompeu et al., 2012). Of the 5 studies with high risk of bias, 3 did not use a randomisation sequence for allocating participants (Costa et al., 2014; Naismith et al., 2013; Nombela et al., 2011), 3 did not blind outcome assessments (Edwards et al., 2013; Nombela et al., 2011; Sammer et al., 2006), and 1 did not conceal participant group allocation (Nombela et al., 2011). Of the 7 studies with unclear risk of bias, 5 did not clearly describe the randomisation sequence generation (Cerasa et al., 2014; Ell, 2013; Pal et al., 2010; París et al., 2011; Pompeu et al., 2012), 3 did not sufficiently describe blinding of outcome assessments (Benninger et al., 2011; Benninger et al., 2012; Ell, 2013), and 2 did not adequately describe concealment of group allocation (Ell, 2013; Pompeu et al., 2012). Only 3 of the cognitive training studies were double-blind (Costa et al., 2014; Pena et al., 2014; Petrelli et al., 2014).

3.7.4 Primary Effect on Executive Function

Ten studies assessed executive functions pre and post-intervention (Benninger et al., 2011; Benninger et al., 2012; Cerasa et al., 2014; Costa et al., 2014; Ell, 2013; Naismith et al., 2013; París et al., 2011; Petrelli et al., 2014; Sammer et al., 2006). Figure 5 shows a forest plot of effect sizes, 95% confidence limits and heterogeneity results.

3.7.4.1 Pooled effect sizes. Pooled effect sizes were calculated for rTMS, combined cognitive training and independently for tailored and standard cognitive training. The pooled effect for rTMS (N = 2) was small (g = .40) and in support for rTMS, yet non-significant (95% CI = -.14 to .93). The pooled effect for combined cognitive training (N = 8) was small (g = .42), statistically significant (95% CI = .15 to .68) and in support of cognitive training. The pooled effect for standard cognitive training (N = 5) was medium (g = .51), statistically significant (95% CI = .16 to .85) and in support of standard cognitive training. Finally, the pooled effect for tailored

cognitive training (N = 3) was small (g = .30) and not statistically significant (95% CI = -.16 to .76). There was no heterogeneity in rTMS, combined and standard pooled effect sizes, I^2 = 0.00%, p >.05. A small and not statistically significant degree of heterogeneity was found in the tailored cognitive training pooled effect, I^2 = 15.49%, p >.05.

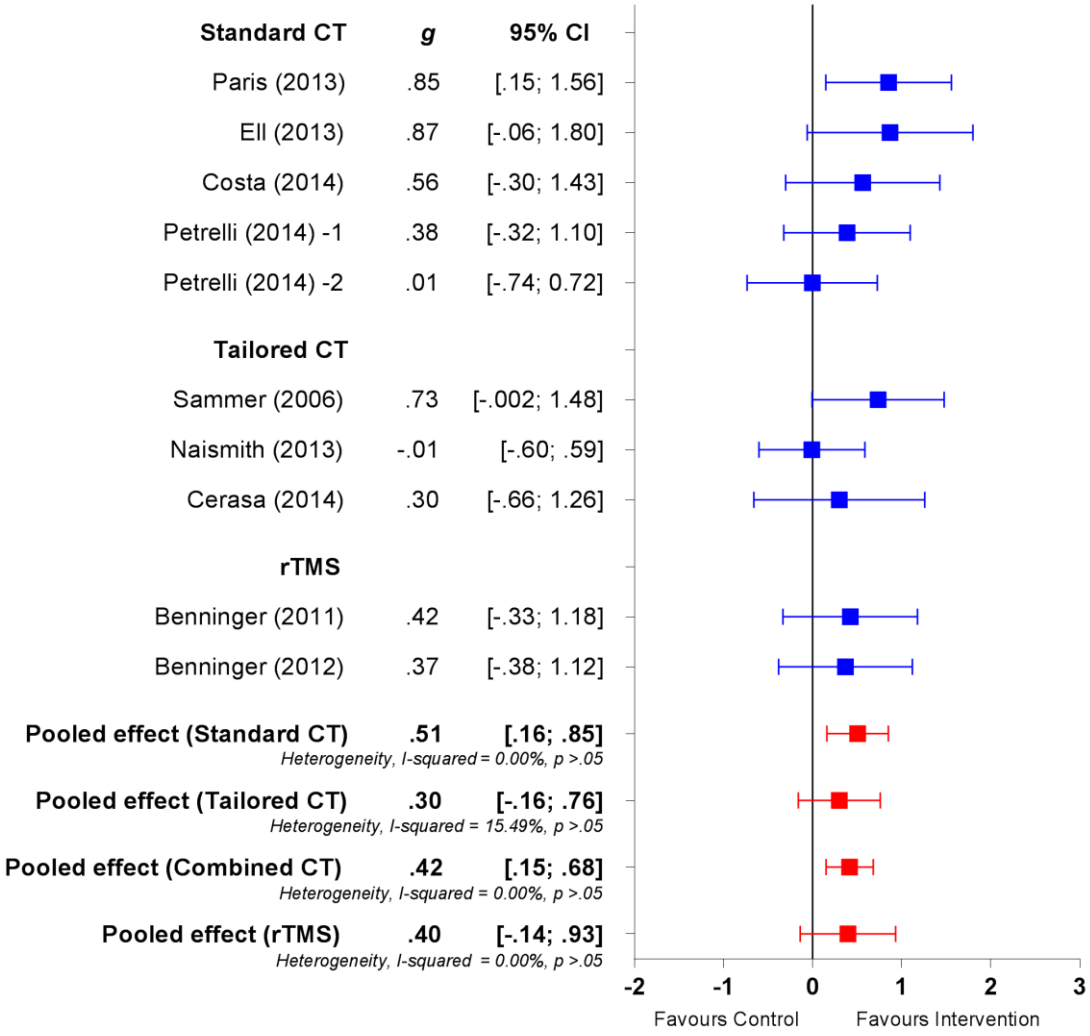

Figure 5. Forest Plot of Effect Sizes for Executive Function.

3.7.5 Secondary Effect on Attention/Working Memory

Eight from 10 cognitive training effects favoured the intervention, ranging from -.33 to .54. However, none were statistically significant. Results are shown in Figure 6.

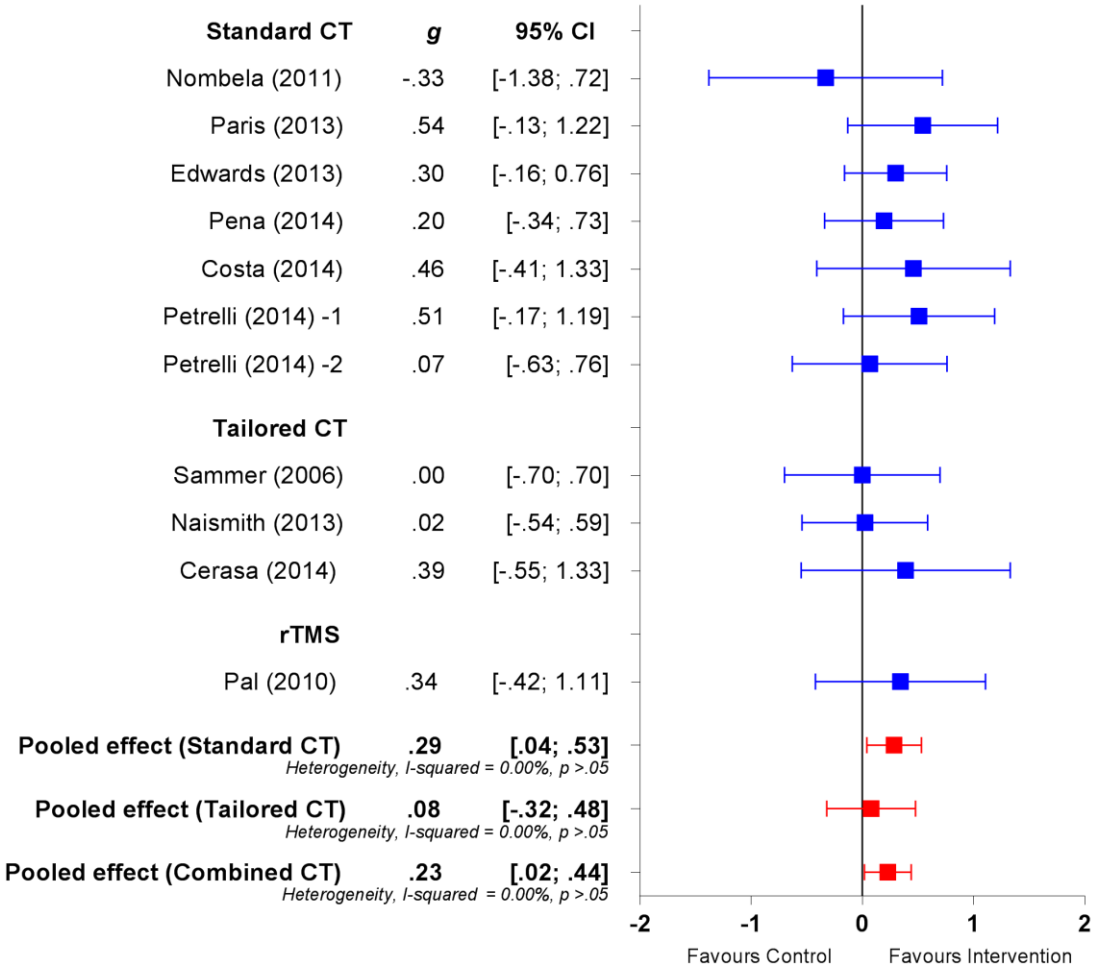

Figure 6. Forest Plot of Effect Sizes for Attention/Working Memory.

3.7.5.1 Pooled effect sizes. One rTMS study (Pal et al., 2010) examining attention/working memory was included in the meta-analysis. Therefore, only combined cognitive training and individual tailored and standard cognitive training pooled effect sizes were calculated. The pooled effect for combined cognitive training (N = 10) supported the intervention with a small (g = .23) and statistically significant effect (95% CI = .02 to .44). The pooled effect for standard cognitive training (N = 7) was also small (g = .29) and statistically significant (95% CI = .04 to .53). Lastly, the pooled effect for tailored cognitive training (N = 3) was very small (g = .08) and not statistically significant (95% CI = -.32 to .48). There was no heterogeneity within combined, standard, or tailored cognitive training effect estimates, I^2 = 0.00%, p >.05.

3.7.6 Secondary Effect on Memory

All studies examining the effect of cognitive training on memory favoured the intervention, with effect sizes ranging .03 to .42 (Cerasa et al., 2014; Naismith et al., 2013; París et al., 2011; Pena et al., 2014; Petrelli et al., 2014). However, no individual effect sizes were statistically significant. Figure 7 provides the results for memory.

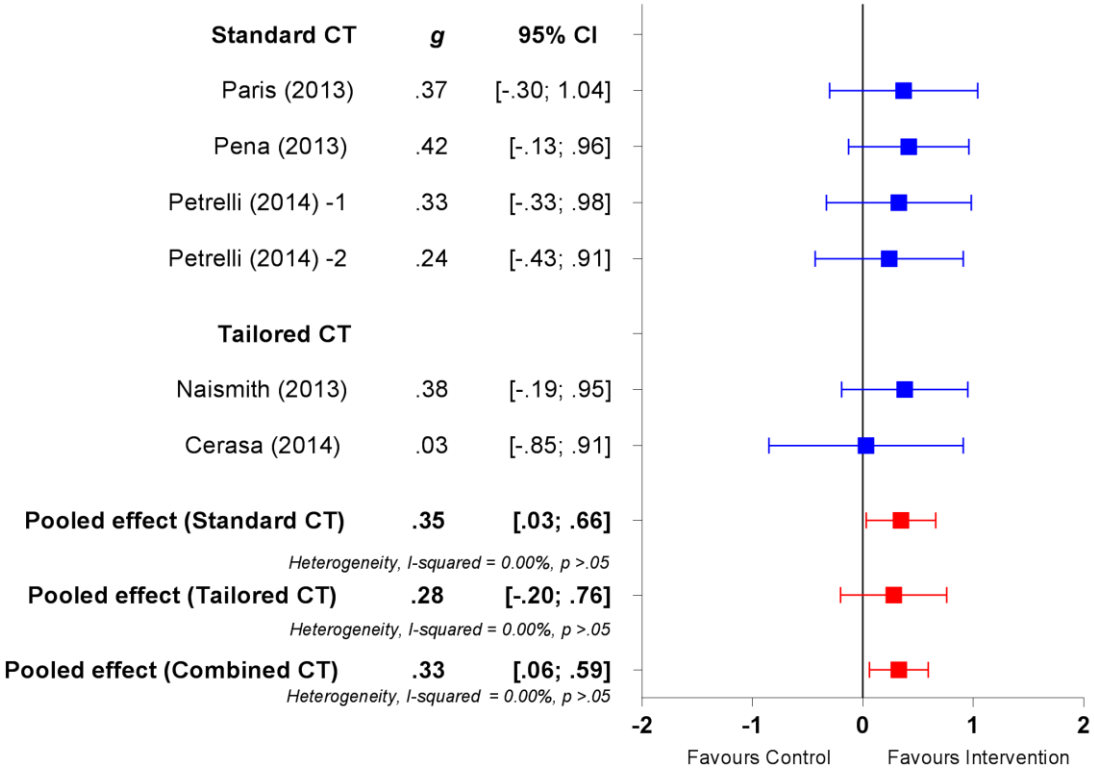

Figure 7. Forest Plot of Effect Sizes for Memory.

3.7.6.1 Pooled effect sizes. No rTMS studies included memory as a primary outcome. Therefore, pooled effect sizes were only calculated for cognitive training studies. The pooled effect for combined cognitive training (N = 6) was small (g = .33) and statistically significant (95% CI = .06 to .59) in support of the intervention. The pooled effect for standard cognitive training (N = 4) was small (g = .35) and statistically significant (95% CI = .03 to .66). In addition, the pooled effect for tailored cognitive training (N = 2) was small (g = .28) and in support for tailored cognitive training, but not statistically significant (95% CI = -.20 to .76). There was no heterogeneity among pooled cognitive training studies, I^2 = 0.00%, p >.05.

3.7.7 Secondary Effect on Visuospatial abilities.

Four studies examined visuospatial abilities (Cerasa et al., 2014; París et al., 2011; Petrelli et al., 2014), with all but Cerasa et al. (2014) supporting the intervention. Results are shown in Figure 8.

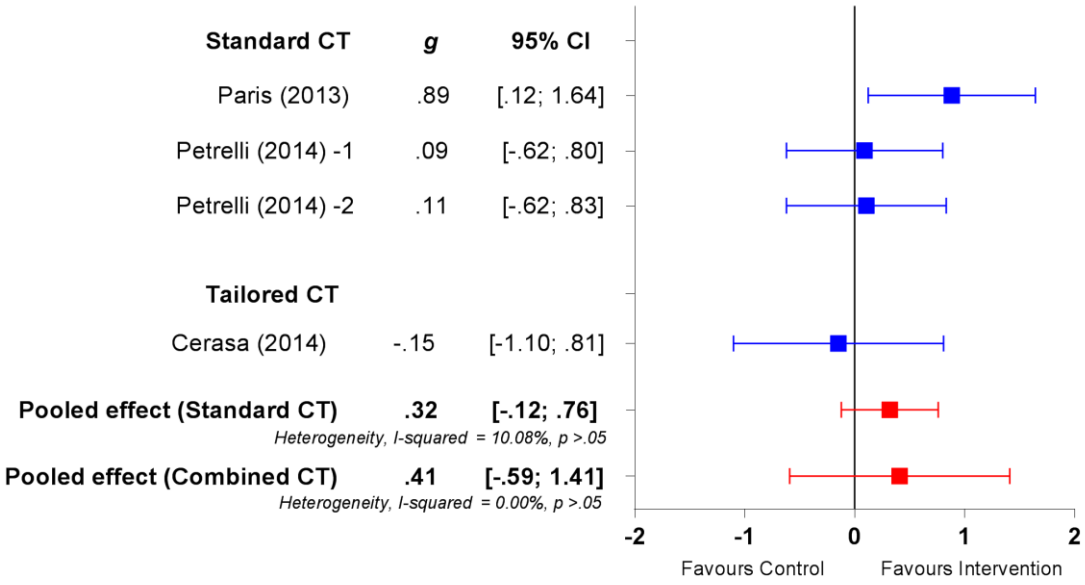

Figure 8. Forest Plot of Effect Sizes for Visuospatial Abilities.

3.7.7.1 Pooled effect size. The pooled effect for combined cognitive training (N = 4) was small (g = .25) and in support for cognitive training, but not statistically significant (95% CI = -.13 to .63). The pooled effect for standard cognitive training was also small (g = .32) and in support of the intervention, but not statistically significant (95% CI = -.12 to .76). There was a small and non-significant degree heterogeneity within the standard cognitive training effect estimate, I^2 = 10.08%, p >.05. No heterogeneity was identified within the combined cognitive training pooled effect, I^2 = 0.00%, p >.05.

3.7.8 Secondary Effect on Global Cognition.

Five studies in this meta-analysis examined the effect of cognitive training on global cognition in PD, with effect sizes between .04 and .48 (Cerasa et al., 2014; París et al., 2011; Petrelli et al., 2014; Pompeu et al., 2012). One rTMS study (Pal et

al., 2010) examined global cognition with results favouring the control group. Figure 9 shows the results for global cognition.

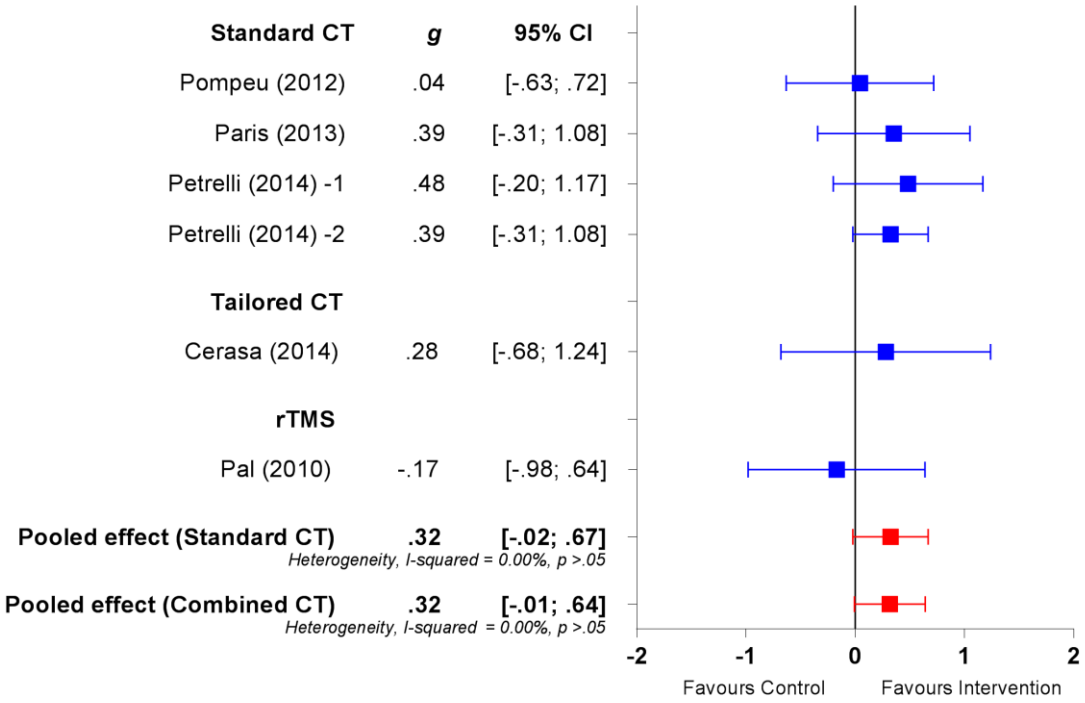

Figure 9. Forest Plot of Effect Sizes for Global Cognition.

3.7.8.1 Pooled effect sizes. The pooled effect for combined cognitive training (N = 5) was small (g = .32) and not statistically significant (95% CI = -.01 to .64). In addition, the pooled effect for standard cognitive training (N = 4) was small (g = .32) and not statistically significant (95% CI = -.02 to .67). There was no heterogeneity within cognitive training effects, I^2 = 0.00%, p >.05.

3.7.9 Publication Bias

Publication bias statistics were calculated for significant, pooled effect sizes by cognitive domain. Despite a non-significant Egger's regression for combined cognitive training effects on executive function, p = 0.25, only 14 non-significant results would be required to render this effect zero, suggesting publication bias. Likewise, Egger's regression for standard cognitive training effects on executive function was not significant (p = 0.54), but needing only 7 non-significant results suggests publication bias. For attention/working memory, Fail-Safe *N*s for combined

cognitive training (N = 2) and standard cognitive training (N = 2) suggest publication bias. However, Egger's regressions were not significant for combined (p = 0.77) or standard training (p = 0.58). Finally for memory, Egger's regression was significant for combined cognitive training (p = 0.006) and only 3 non-significant results would be needed to undermine this significant pooled effect. Also for memory, Egger's regression for standard cognitive training effects was not significant (p = 0.27), yet a low Fail-Safe N (N = 1) suggests publication bias.

3.7.10 Sensitivity Analyses

Petrelli et al. (2014) reported means and standard error values adjusted for covariates and not raw data, Sammer et al. (2006) did not report pre/post data and effect sizes were computed using probability values from post-intervention outcomes, and Ell (2013) conducted a short cognitive training intervention (8 minutes) compared to the longer interventions included in this meta-analysis. Therefore, three sensitivity analyses were conducted to determine if removing these studies would significantly impact pooled effect estimates. After removing Petrelli et al. (2014), the pooled effect for combined cognitive training (N = 6) on executive function increased to medium (g = 0.50) and statistically significant (95% CI 0.19 to 0.81). Standard cognitive training (N = 3) remained medium (g = 0.77) and statistically significant (95% CI 0.30 to 1.24). For attention and working memory, the pooled effect for combined cognitive training (N = 8) remained small (g = 0.22) but reduced to not significant (95% CI -0.01 to 0.45). Attention/working memory effects for standard cognitive training (N = 5) remained small (g = 0.29) and statistically significant (95% CI 0.004 to 0.57). For memory, the effect for combined cognitive training (N = 4) remained small (g = 0.35) and statistically significant (95% CI 0.03 to 0.66). The memory effect for standard cognitive training (N = 2) remained small (g = 0.40) and reduced to not significant (95% CI -0.02 to 0.82). For visuospatial function, the effect for combined cognitive training (N = 2) remained small (g = 0.37) and not significant (95% CI -0.52 to 1.25). Standard cognitive training (N = 1) increased to medium (g = 0.76) and statistically significant (95% CI 0.05 to 1.48). For global cognition the effect for combined cognitive training (N = 3) remained small (g = 0.22) and reduced to not significant (95% CI -0.21 to 0.66),

while standard cognitive training (N = 2) remained small (g = 0.21) and not significant (95% CI -0.28 to 0.70).

After removing Sammer et al. (2006), the pooled effect for combined cognitive training (N = 7) on executive function remained small (g = 0.37) and statistically significant (95% CI 0.08 to 0.66). Tailored cognitive training (N = 2) remained small (g = 0.08) and not significant (95% CI -0.43 to 0.58). For attention and working memory, the pooled effect for combined cognitive training (N = 9) remained small (g = 0.25) and statistically significant (95% CI 0.04 to 0.47). Attention/working memory effects for tailored cognitive training (N = 2) remained small (g = 0.12) and not significant (95% CI -0.36 to 0.60). Lastly, after removing Ell (2013) from the pooled effect for combined cognitive training (N = 7) on executive function, the effect size remained small (g = 0.38) and statistically significant (95% CI 0.10 to 0.65). Standard cognitive training (N = 4) reduced to small (g = 0.45) but remained statistically significant (95% CI 0.07 to 0.82).

3.7.11 Meta-Regression Analysis

According to Borenstein et al. (2011) a minimum of 10 studies per moderator variable is required before conducting meta-regression. Age, years of education, duration of illness, and length of intervention were identified as potential moderators of effect estimates. However, meta-regression of four moderator variables would require 40 studies to be included in each pooled effect. Therefore, meta-regression was not completed in this meta-analysis.

3.8 Discussion

3.8.1 Main Findings

This meta-analysis is the first to provide distinct pooled effect sizes for standard and tailored cognitive training and rTMS interventions for cognition in PD. When considered together, standard and tailored cognitive training studies appear to improve executive function, albeit only by a small amount (g = .42; 95% CI = .15 to .68). When analysed separately, perhaps because of the small number of studies, executive function was no longer improved by tailored cognitive training (g = .30,

95% CI = -.16 to .76), but standard cognitive training appeared to have a more moderate effect (g = .51, 95% CI = .16 to .85). This nonsignificant effect for tailored cognitive training may represent a Type II error, given that a small effect size was observed but only three tailored cognitive training studies were included in this meta-analysis. There were insufficient studies for a formal comparison of the relative effects of standard and tailored cognitive training. Thus more controlled trials of tailored cognitive training are needed to determine if this modality is more or less efficacious than a standard intervention. Executive function did not appear to improve (g = .40, 95% CI = -.14 to .93) in the two rTMS studies investigated (Benninger et al., 2011; Benninger et al., 2012). Given that preliminary results of controlled (Pal et al., 2010) and uncontrolled (Boggio et al., 2005) rTMS trials report improvements in cognition, more detailed exploration of this therapeutic technique is required.

People with PD and cognitive impairment demonstrate deficits in attention/working memory (Cholerton et al., 2014). When considered together, attention/working memory was improved by standard and tailored cognitive training (g = .23, 95% CI = .02 to .44) and by standard training alone (g = .29, 95% CI = .04 to .53). This finding conflicts with those of Leung et al. (2015) who reported a medium and significant effect for working memory, but a small and non-significant negative effect for attention. Unlike this meta-analysis, however, Leung et al. (2015) included one study that had a large negative effect on attention (Zimmermann et al., 2014). This study compared computerised cognitive training (intervention group) to computerised sport-related video gaming (control group), but sport-related video games have improved cognition in older adults (Basak, Boot, Voss, & Kramer, 2008), which Zimmermann et al. (2014) also reported. Inclusion of this study in the previous meta-analysis led to inclusion of a large negative effect for cognitive training on attention, but inversely included a large positive effect for computerised sport-related gaming on attention (rather than an effect favouring a control group). The current meta-analysis excluded this study to ensure only controlled comparisons were included in pooled effects, and this approach found positive effects for combined and standard cognitive training improving attention/working memory in PD.

Only one controlled rTMS study (Pal et al., 2010) examined attention/working memory in PD and this study produced a small and non-significant effect (g = .34, 95% CI = -.42 to 1.11). However, several uncontrolled rTMS studies have shown improvements in cognition (Epstein et al., 2007; Fregni et al., 2004; Furukawa et al., 2009; Srovnalova et al., 2011). Before concluding whether rTMS is or is not helpful in alleviating cognitive deficits in PD, more controlled rTMS studies are needed.

Whilst the primary cognitive impairments in PD are characterised by frontal dysfunction, memory impairment is also common (Domellof, Ekman, Forsgren, & Elgh, 2015). Both standard and combined cognitive training studies offered small improvements in memory (standard: g = .35, 95% CI = .03 to .66; combined: g = .33, 95% CI = .06 to .59). This corresponds with a meta-analysis of memory training in healthy older adults, which found significant memory improvements post-training (Zehnder et al., 2009).

Due to the heterogeneous nature of cognitive impairment in PD, individuals may demonstrate deficits in visuospatial and language domains (Cholerton et al., 2014). There was no impact of cognitive training on visuospatial abilities across the four studies examined in this analysis (combined: g = .25, 95% CI = -.13 to .63; standard: g = .32, 95% CI = -.12 to .76). No controlled studies evaluated language impairment. Although language deficits are rare in PD, recent research suggests impaired functioning in language and visuospatial domains (Goldman et al., 2013). For that reason, future studies should include standardised neuropsychological assessment of these domains, in line with MDS Task Force recommended tests (Litvan et al., 2012).

The final outcome of this meta-analysis was global cognition, which showed small and non-significant effects for both combined (g = .32, 95% CI = -.01 to .64) and standard cognitive training (g = .32, 95% CI = -.02 to .67). This is not consistent with the finding of improved global cognition following cognitive training for those with MCI (Li et al., 2011). Compared to larger cognitive training trials improving all cognitive domains in healthy older adults (Lampit, Hallock, & Valenzuela, 2014), the presently included studies may have been underpowered (i.e., small *N*) which

resulted in non-significant effects. Future studies need to recruit larger samples to ensure sufficient statistical power in cognitive training trials in PD.

In addition to the cognitive outcomes, sensitivity analyses examined whether removing Petrelli et al.'s (2014) covariate adjusted results impacted corresponding effect estimates. The effect of combined cognitive training on executive function remained significant, even increasing slightly, and the effect of standard cognitive training on visuospatial function increased to medium and statistically significant. However, the effect of combined cognitive training on attention/working memory and standard cognitive training on memory, reduced to non-significance. These variations suggest that this study's adjusted results had a large impact on attention/working memory, visuospatial, memory and global cognition effects (Petrelli et al., 2014). Pooling effect sizes with adjusted results may not, however, demonstrate an accurate effect of standard cognitive training on these cognitive domains in PD. Adjusting results for the effect of covariates will likely under-represent the true effect of an intervention (e.g., cognitive training), by accounting for a proportion of variance in outcome variables. Sensitivity analyses also examined whether removing Sammer et al.'s (2006) effect sizes (computed with probability statistics) or Ell's (2014) results from a short cognitive training intervention, would impact pooled effect estimates. No changes in statistical significance of effects were observed.

3.8.2 Limitations and Directions for Future Research

There are some limitations to this meta-analysis. Most studies selected neuropsychological tests representative of each intervention's proposed mechanism of action (i.e., cognitive training to improve executive function matched with executive function tests as primary outcomes). However, Cerasa et al. (2014) used a domain-specific intervention (attention) and measured pre/post performance in other cognitive domains (e.g., visuospatial abilities). This study measured a cognitive domain that was not theoretically related to the domain-specific intervention, which may have contributed to the non-significant pooled effect size for visuospatial abilities. This result suggests the effect of cognitive training may have been specific to the domain targeted by the intervention.

For rTMS, methodological differences between studies may have resulted in the initial nonsignificant effect for executive function. Benninger et al. (2011) administered 50 Hz intermittent theta burst rTMS over the primary motor and dorsolateral prefrontal cortices, whereas Benninger et al. (2012) applied 50 Hz rTMS over primary motor cortices. Both studies were sham-controlled but delivered fewer than 10 minutes of stimulation and differed in type of stimulation and target locations. Compared to the short-term effects found in rTMS studies, intermittent theta burst rTMS has been shown to increase the duration of synaptic plasticity by delivering three shorter pulses of stimulation (every 200 milliseconds) to specific neuronal groups (Huang, Edwards, Rounis, Bhatia, & Rothwell, 2005). Conversely, earlier studies delivered longer stimulation (20 to 30 minutes) and showed significant improvements in cognition in PD (Boggio et al., 2005; Fregni et al., 2004; Pal et al., 2010). Length and frequency of stimulation may, therefore, produce variable effects on synaptic connections and associated cognitive functions. Moreover, Benninger et al. (2012) assessed executive function but stimulated primary motor cortices not associated with executive function improvement. Having said this, rTMS has been shown to be relatively nonfocal, often activating a combination of cortical systems that may have interacting effects (Huang et al., 2005). In their earlier study, Benninger et al. (2011) used the 5 cm rule to target the dorsolateral prefrontal cortex, which provides widespread stimulation across motor and prefrontal sites (Pascual-Leone, Wassermann, Grafman, & Hallett, 1996). Consequently, rTMS over primary motor cortices may activate broader cortical systems that impact prefrontal areas (thus affecting executive function). Despite these differences, both studies reported positive effects in support of rTMS for improving cognition in PD. Future studies should build on these preliminary results by exploring the therapeutic potential of this non-invasive intervention for people with cognitive impairment and PD.

A lack of sensitivity of executive function and attention/working memory measures for detecting change in PD may also have contributed to the null rTMS pooled effect sizes. For Pal et al. (2010), the Trail Making Test-Part A (TMT-A) was one of three outcomes used to compute an attention/working memory effect (Reitan, 1992). However, a meta-analysis comparing TMT-A performance between people with frontal deficits to those with posterior deficits found no significant difference between groups (Demakis, 2004). This suggests the TMT-A is unable to discriminate

between frontal and nonfrontal cognitive impairments, yet impairments in PD are associated with deficits in prefrontal (dorsolateral and ventrolateral) cortices (Lewis, Dove, Robbins, Barker, & Owen, 2003). In addition, both rTMS (Benninger et al., 2011; Benninger et al., 2012) studies assessing executive function used the Frontal Assessment Battery (FAB) (Dubois, Slachevsky, Litvan, & Pillon, 2000). The FAB has, however, low sensitivity (66.3%) in detecting executive function impairments related to dementia in PD (Kaszás et al., 2012). Also, neither participant group were classified as cognitively impaired which may have resulted in a ceiling effect when administering rTMS to produce improvements in cognition in PD. These limiting factors may account for the non-significant executive function and attention/working memory effect estimates and must be acknowledged when interpreting the results.

A further limitation was the heterogeneous application of neuropsychological tests for cognitive outcomes in the current literature. Test selection bias was accounted for in the present study by first coding all tests from each study into cognitive domains, computing composite domain effects and adjusting for intercorrelations between tests, then pooling effects. This method included 65 neuropsychological tests across pooled effect sizes. Borenstein et al. (2011) recommends using this method to pool effects when studies report multiple conceptually related outcomes. However, conceptually related outcomes must be adjusted for high intercorrelations, which produce a less precise estimate of a pooled effect. It is recommended that future studies adopt a more homogenous use of neuropsychological tests (e.g., MDS Task Force recommended tests; Litvan et al., 2012) to reduce the impact of multiple outcomes in meta-analysis and improve the precision of future pooled effects.

Variable length of cognitive training interventions also limited this meta-analysis. Jean, Bergeron, Thivierge, and Simard (2010) recommend 6 to 20 cognitive training sessions (up to 15 hours) completed within 12 weeks to be most effective, when compared to longer and more costly interventions. However, included studies ranged between 8 minutes (computer-based rule learning task; Ell, 2013) and 45 hours (Sudoku puzzle every day for 6 months; Nombela et al., 2011). Having said this, removing Ell (2013) from pooled effects resulted in no changes in corresponding effect estimates and recent cognitive training studies have

implemented more homogenous interventions (9 to 18 hours; Costa et al., 2014; Pena et al., 2014; Petrelli et al., 2014). Future trials need to build upon current scientific evidence to establish the most efficacious parameters (e.g., length, frequency, and type of training) for cognitive interventions in PD.

The literature relating to the impact of either rTMS or tDCS in PD on cognitive function is limited, and very few studies employed a controlled design. In addition to a small *N*, there was evidence of bias within trials and bias in publication for combined and standard cognitive training effects on executive function, attention/working memory, and memory. Although violation of Rosenthal's Fail-Safe *N* suggests included studies may not be a true representation of the population effect, 13,162 studies were systematically searched in published and unpublished databases and only 14 met inclusion criteria. This extensive search, inclusive of grey literature, suggests these significant Fail-Safe *N* results may not be an accurate indication of publication bias.

This study highlights the need for controlled trials of cognitive training (standard and tailored), rTMS, and tDCS for improving cognition in PD. Future studies need to conduct randomised controlled trials in accordance with the CONSORT statement to provide reliable and externally valid evidence of these nonpharmacological interventions (Boutron, Moher, Altman, Schulz, & Ravaud, 2008). Future interventions need to compare standard (not individualised) and tailored (individualised) cognitive training, and examine whether combining cognitive training with brain stimulation further improves cognition in PD. Studies should also compare interventions between participant groups with varying severity of cognitive impairment, to provide insight into which stages of disease progression are most likely to benefit from cognitive training and brain stimulation. In addition, future studies need to include activities of daily living and quality of life as primary outcomes (Klepac et al., 2008).

3.9 Chapter Summary

This meta-analysis builds upon previous results to provide the first individual pooled effect sizes for standard and tailored cognitive training and brain stimulation interventions for cognition in PD. Despite the significant prevalence of cognitive impairment in PD, there is a considerable lack of empirical evidence to support the improvement of cognitive functioning. An extensive literature search uncovered 14 controlled trials, three rTMS, three tailored cognitive training, and eight standard cognitive training. The only controlled trial of tDCS did not provide sufficient data for inclusion. Based on the available studies, there is evidence to support the use of standard and tailored cognitive training for improving executive function, attention/working memory, and memory in PD. More controlled cognitive training, rTMS, and tDCS interventions are needed to establish a reliable and valid estimate of their therapeutic potential in PD. Although limited by available studies, the results of this meta-analysis provide a promising starting point for future nonpharmacological interventions in PD.

The next chapter will examine the efficacy of cognitive training and tDCS interventions for improving cognition, activities of daily living, and quality of life in PD-MCI.

CHAPTER 4 Study 3. A Pilot-Randomised Controlled Trial of Cognitive Training and Transcranial Direct Current Stimulation in Parkinson's Disease-Mild Cognitive Impairment

4.1 Introduction

Over the past five years, there has been a considerable increase in research examining cognitive impairments in PD and the potential of nonpharmacological interventions (e.g., cognitive training and non-invasive brain stimulation) for improving cognitive function in people with PD and PD-MCI (Goldman & Weintraub, 2015). It remains unknown whether cognitive training (standard or tailored), transcranial direct current stimulation (tDCS), or cognitive training (standard or tailored) combined with tDCS is most efficacious for improving cognition in this population.

This chapter presents the findings of the first randomised controlled trial of standard cognitive training, tailored cognitive training, tDCS, standard cognitive training + tDCS, and tailored cognitive training + tDCS for improving cognition, activities of daily living, and quality of life in people with PD-MCI. The first half of this chapter outlines the study methodology, followed by the results and a thorough discussion of the findings with recommendations for future clinical trials.

Overall, statistically significant improvements in executive function, attention/working memory, memory, language, activities of daily living, and quality of life were observed across and/or within intervention groups. The results suggest a theoretically additive benefit for combining cognitive training with tDCS to improve

cognition and practical outcomes in PD-MCI. However, several outcomes did not respond to intervention effects and the implications of this are discussed.

4.2 Methodology

4.2.1 Research Design and Study Setting

This study was a randomised controlled trial (RCT) comparing standard cognitive training, tailored cognitive training, tDCS, standard cognitive training + tDCS, and tailored cognitive training + tDCS against a control group, to determine which modality was more efficacious for improving cognition, quality of life and activities of daily living in PD. The study was completed in the School of Psychology and Speech Pathology at Curtin University, Perth, Western Australia. Participant recruitment, neuropsychological testing and interventions were completed between March and December 2015. Data was collected at pre-intervention, post-intervention (Week 5), and follow-up (Week 12). This study was conducted in accordance with the CONSORT requirements for nonpharmacological interventions (Boutron et al., 2008).

4.2.2 Participants

4.2.2.1 Inclusion and exclusion criteria. Participants were adults (> 18 years of age) with PD living in Western Australia. The following inclusion criteria was used: (1) participants diagnosed with idiopathic PD by a neurologist or geriatrician in accordance with the United Kingdom Parkinson's Disease Society Brain Bank Clinical Diagnostic criteria, (2) presence of MCI in accordance with the MDS PD-MCI Level II diagnostic criteria (from Chapter 2), (3) a stable response to antiparkinsonian medication for a minimum period of 2 months preceding the study, and (4) cognitive deficits that do not interfere with functional independence.

As for Chapter 2, the same exclusion criteria applied to this study with exception of additional tDCS exclusion conditions. Participants were excluded from the study on the basis of the following criteria: (1) presence of PD-Dementia (TICS total score < 12) (2) recent history of brain surgery, (3) Deep Brain Stimulation (DBS) implant, (4) active skin disease on the scalp, (5) history of migraine, (6)

history of epilepsy, (7) unstable medical condition (e.g., uncontrolled diabetes), (8) history of asthma, (9) metal implants in the head/brain, and (10) currently using a hearing aid. All participants who met inclusion/exclusion criteria provided informed consent prior to participation in this study.

4.2.3 Interventions

4.2.3.1 Cognitive training. The website version of Smartbrain Pro™ (www.smartbrain.net) was used for cognitive training. Smartbrain Pro™ is an interactive computer-based cognitive training program designed to train each cognitive domain (executive function, attention/working memory, memory, language and visuospatial abilities). Smartbrain Pro™ has been used in trials which have demonstrated improvements in global cognitive functioning in AD (Tárraga et al., 2006), and improvements in attention, information processing speed, memory, visuospatial abilities, verbal fluency, and executive functions in PD (París et al., 2011).

4.2.3.2 Standard cognitive training and standard cognitive training + tDCS groups. Participants in the standard cognitive training and standard cognitive training + tDCS groups completed a pre-determined program comprising of 10 activities. Each cognitive domain was trained by two activities per domain (see Table 5).

Table 6

Smartbrain Pro™ Activities for Standard and Tailored Cognitive Training

Cognitive Domain	Training Activity
Memory	1. Remembering faces 2. Remembering words
Attention / Working Memory	3. Finding symmetries 4. Finding letters
Language	5. Finishing sentences 6. Relationships between words
Executive Function	7. Ordering the steps of an action 8. Similarities and differences
Visuospatial	9. Identifying coordinates 10. Clicking static items

4.2.3.3 Tailored cognitive training and tailored cognitive training + tDCS groups. Participants in the tailored cognitive training and tailored cognitive training + tDCS groups completed the same activities as the standard cognitive training groups. However, activities in the tailored groups were customised to each participant's pre-intervention neuropsychological test results. For example, a participant who demonstrated memory and executive function impairment at pre-intervention, completed only two memory and two executive function activities on Smartbrain Pro™.

4.2.3.4 Brain stimulation. tDCS was used as the brain stimulation intervention. tDCS is a noninvasive brain stimulation procedure delivering low intensity electrical currents (0.5 mA to 2mA) to specific cortical regions in the brain (Creutzfeldt et al., 1962; Nardone et al., 2012). tDCS modulates neuronal activity, with anodal tDCS used to increase excitability and cathodal tDCS decreases excitability in the cortex.

4.2.3.6 tDCS, standard cognitive training + tDCS, and tailored cognitive training + tDCS groups. In addition to the cognitive training, participants allocated to the tDCS, standard cognitive training + tDCS, and tailored cognitive training + tDCS groups completed 4-sessions of tDCS stimulation over 4-weeks (one session per week).

4.2.3.7 Control group. Participants in the control group completed post-intervention and 12-week follow-up neuropsychological assessments, but they did not complete cognitive training or tDCS interventions. Participants in the control group were provided with the opportunity to complete cognitive training or tDCS when the study was complete. Table 6 provides a summary of the parameters of each intervention.

4.2.4 Procedure

4.2.4.1 Ethical and clinical registration. Curtin University's Human Research Ethics Committee provided ethical approval prior to study commencement (Approval number: HR 189/2014). This study was also registered with the Australian

New Zealand Clinical Trials Registry (ANZCTR: 12614001039673).

4.2.2.2 Recruitment. Participants were given the opportunity to participate in this study if they met the MDS Task Force diagnostic criteria for PD-MCI and tDCS inclusion criteria.

4.2.4.3 Randomisation. To limit selection bias, a computer-generated randomisation list was used to allocate participants to groups using block randomisation at a ratio of 1:1 (Schulz & Grimes, 2002). Participants in the cognitive training and tDCS groups were informed of intervention start dates and participants in the control group were advised of a 4-week waiting period before a second neuropsychological assessment (post-intervention). Following post-intervention assessments, participants completed the 12-week follow-up assessments.

4.2.4.4 Cognitive training format. Jean et al. (2010) suggest that for people with mild cognitive impairment, 6 to 20 cognitive training sessions completed in less than 12 weeks are as efficacious as longer and more costly interventions. Smartbrain Pro™ creators also suggest that participants may experience fatigue after 35 to 45 minutes of cognitive training which may impact their performance (www.smartbrain.net). Cognitive training groups completed three 45-minute in-home training sessions each week for 4-weeks (total of 12 sessions). Participants were requested to structure their training sessions each week. For example, completing cognitive training on Mondays, Wednesdays and Fridays. Participants were asked to complete training sessions in a quiet location free from distractions. Each participant was provided with a unique 'USER ID' and 'PASSWORD' to log into the training program. Smartbrain Pro™ was streamed directly from the internet onto participant's home computers or onto Acer™ Aspire E3-112 portable computers via Optus™ E5251 Mini Wifi Modems (provided by the researcher). Following completion of each 45-minute training session, the program terminated. Performance was automatically monitored by the program to adjust individual difficulty levels for each activity. For example, if a participant scored one incorrect answer on Level 5 of an executive function activity, the program decreased the difficulty of that activity to Level 4 in the following rotation. Conversely, if a participant scored all correct answers on Level 5, the program increased the difficulty of that activity to Level 6 in

the following rotation. Participants began the program on ‘Level 1’ (least challenging) and progressed through the levels to a maximum of ‘Level 15’ (most challenging).

On the first day of each intervention the researcher visited participants’ homes to set up the program (and equipment if necessary), ensure the program was working appropriately, and provide written and verbal instructions. Participants were instructed to contact the researcher if they required assistance with the program, or if they experienced technical difficulties with the software during the intervention. All participant homes were within a 70 kilometer radius of Perth metropolitan area.

4.2.4.6 Brain stimulation format. Four sessions of anodal tDCS, one per week for 4-weeks, were administered to participants in the tDCS groups. Stimulation session times were arranged individually and scheduled for the same day and time each week. During each session, participants completed 20 minutes of constant current 1.5 mA stimulation over the left dorsal lateral prefrontal cortex. tDCS was delivered using the TCT^{TM} tDCS stimulator (http://www.trans-cranial.com/) and administered with two 50 x 70 mm^2 sponge electrodes, soaked in saline solution. There was a period of 30 seconds at the start and end of the tDCS for ramp up/ramp down of the stimulator.

To stimulate the left dorsal lateral prefrontal cortex, the anode electrode was placed over F3 according to the 10–20 international system for EEG electrodes placement (see Figure 10). The F3 anode location was determined by measuring over a participant’s centre line of their scalp, from the Inion (occipital protuberance) to the Naison (bridge of the nose), recording the total length, then using a felt-tip pen to mark the centre point of that length on the scalp. The researcher then measured over the mark on the scalp from a participant’s right preauricular point (middle of the ear) to their left preauricular point and marked the middle of that length on their scalp. This central point is known as ‘Cz’ and was used to locate F3. From Cz, 20% of the total Naison to Inion length was measured toward the front of the scalp and marked as ‘Fz’. From Fz, 20% of the preauricular to preauricular length was measured to the left of the scalp and marked as F3, the anode electrode location. The cathode electrode was placed on the forehead above the left eye to ensure stimulation was

delivered to the left dorsal lateral prefrontal cortex. The 10–20 system of electrode placement has been used in tDCS studies (Boggio et al., 2006; Doruk et al., 2014) and is established as an accurate method of localization by neuronavigation techniques (Herwig, Satrapi, & Schönfeldt-Lecuona, 2003). tDCS sessions were completed at Curtin University's Neuroscience Laboratory.

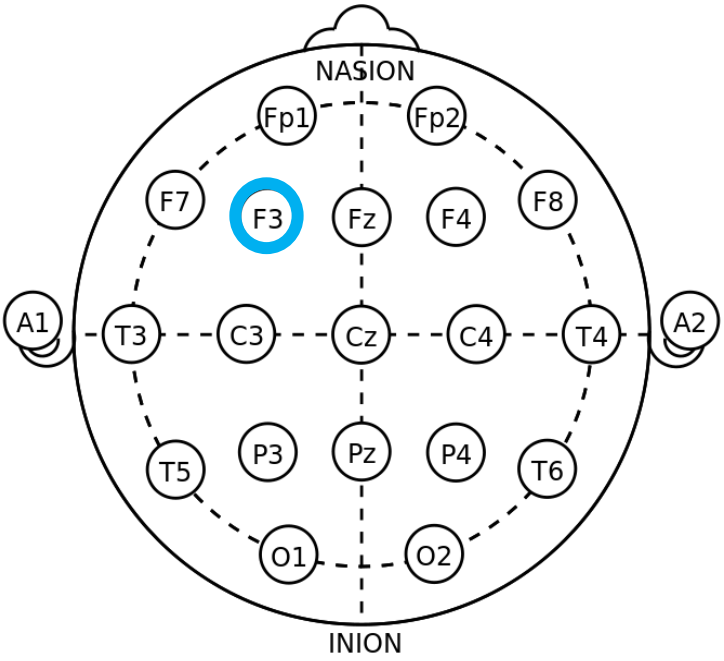

Figure 11. The 10–20 International System for EEG Electrodes Placement

4.2.4.7 Data collection. The neuropsychological assessments conducted in Chapter 2 were used as pre-intervention (Week 0) results. Identical assessments were conducted post-intervention (Week 5) and follow-up (Week 12). All neuropsychological assessments, cognitive training, and brain stimulation were completed during participants' 'ON' stage of medication use, to ensure they were feeling their best. Participants were reimbursed for travel costs and given a $10 gift card for completing pre-intervention assessments and a $15 gift card for completing the intervention and follow-up assessments.

4.2.5 Outcomes

4.2.5.1 Measures. Neuropsychological assessment measures for this study were the same as for Chapter 2 and were used at the post-intervention and 12-week follow-up assessments. Recommended by the MDS Task Force (Litvan et al., 2012), the following measures were used to assess outcome variables: (1) *executive function* was assessed with the Stockings of Cambridge (SOC) subtest from the Cambridge Neuropsychological Test of Automated Batteries (CANTAB^{TM}) and the phonemic verbal fluency subtest of the Controlled Oral Word Association Task (COWAT), (2) *attention and working memory* was assessed with the Letter-Number Sequencing (LNS) subtest from the Wechsler Adult Intelligence Scale-IV (WAIS-IV) and the Stroop (Colour-Word) Test, (3) *memory* was assessed with the Hopkins Verbal Learning Test-Revised (HVLT-R) immediate recall subtest and the Paragraph Recall subtest of the Rivermead Behavioural Memory Test (RMBT), (4) *visuospatial abilities* were assessed with the Judgement of Line Orientation (JLO) test and the Hooper Visual Organisation Test (HVOT), and (5) language was assessed with the Boston Naming Test-Short Form (BNT-Short Form) and the Similarities subtest from the WAIS-IV battery. Global cognition was assessed with the Parkinson's Disease – Cognitive Rating Scale (PD-CRS) and the Mini Mental State Examination (MMSE). Premorbid intelligence and activities of daily living were assessed by the Australian version of the National Adult Reading Test (AUSNART) and Unified Parkinson's Disease Rating Scale (section II), respectively. As measured in Chapter 2, depression was assessed by the depression subscale of the DASS-21 and pre-intervention scores were included as covariates. In addition to cognitive and practical outcomes, quality of life was assessed using the measure described below.

4.2.5.3 Health-related quality of life. The *Parkinson's Disease Questionnaire-39* (PDQ-39) was used to measure quality of life (Peto, Jenkinson, & Fitzpatrick, 1998). The PDQ-39 contains 39 items assessing eight health-related dimensions: mobility, daily living, emotional wellbeing, stigma, social support, cognition, communication and bodily discomfort. Participants were asked, "*Due to having Parkinson's Disease, how often during the last month have you…"* and rated the impact of their PD symptoms on their experiences in daily life. Example items include *"Had difficulty carrying bags of shopping?"* and *"Avoided situations which involve eating and drinking in public?"*. A summary index score was used as the

outcome variable for the PDQ-39 and was calculated by dividing the sum total of the eight dimension scores by eight (Jenkinson, Fitzpatrick, Peto, Greenhall, & Hyman, 1997). Summary index scores range between 0 (no problems with quality of life) and 100 (maximum problems with quality of life). The PDQ-39 has shown strong internal consistency across the eight dimensions (α = .72 to .95), as well as strong test-retest (r = .76 to .93) reliability coefficients (Hagell & Nygren, 2007).

4.3 Hypotheses

H1: Compared to participants in the Control group, participants in the Standard Cognitive Training, Tailored Cognitive Training, tDCS, Standard Cognitive Training + tDCS, and Tailored Cognitive Training + tDCS groups will demonstrate statistically significantly larger improvements in (i) cognitive functioning, (ii) ADL, and (iii) QOL, from pre-intervention (Time 1) to post-intervention (Time 2), and pre-intervention to three-month follow-up (Time 3) assessments.

H2: Compared to participants in the Standard Cognitive Training group, participants in the Tailored Cognitive Training, tDCS, Standard Cognitive Training + tDCS, and Tailored Cognitive Training + tDCS groups will demonstrate statistically significantly larger improvements in (i) cognitive functioning, (ii) ADL, and (iii) QOL, from pre-intervention (Time 1) to post-intervention (Time 2), and pre-intervention to three-month follow-up (Time 3) assessments.

H3: Compared to participants in the Tailored Cognitive Training group, participants in the tDCS, Standard Cognitive Training + tDCS, and Tailored Cognitive Training + tDCS groups will demonstrate statistically significantly larger improvements in (i) cognitive functioning, (ii) ADL, and (iii) QOL, from pre-intervention (Time 1) to post-intervention (Time 2), and pre-intervention to three-month follow-up (Time 3) assessments.

H4: Compared to participants in the tDCS group, participants in the Standard Cognitive Training + tDCS and Tailored Cognitive Training + tDCS groups will demonstrate statistically significantly larger improvements in (i) cognitive functioning, (ii) ADL, and (iii) QOL, from pre-intervention (Time 1) to post-intervention (Time 2), and pre-intervention to three-month follow-up (Time 3) assessments.

H5: Compared to participants in the Standard Cognitive Training + tDCS group, participants in the Tailored Cognitive Training + tDCS group will demonstrate statistically significantly larger improvements in (i) cognitive functioning, (ii) ADL, and (iii) QOL, from pre-intervention (Time 1) to post-intervention (Time 2), and pre-intervention to three-month follow-up (Time 3) assessments.

4.4 Data analysis

4.4.1 Statistical Hypothesis Testing

Generalised linear mixed models (GLMMs) were used to test statistical hypotheses (Bryk & Raudenbush, 1987). All GLMMs were performed using a syntax file procedure in SPSS 22.0. GLMMs control for outcome variables with non-normal distributions and include both random and fixed effects (McCulloch, 2006). For the present study, there was one random effect (participant) and three fixed effects: Group (standard training vs tailored training vs tDCS vs standard training + tDCS vs tailored training + tDCS vs control), time (pre, post, follow-up) and the Group x Time interaction (McCulloch, 2006). Separate GLMMs were run for each outcome variable to optimise the likelihood of convergence (McCulloch, 2006). Independently analysing outcome variables increased the Type 1 error rate. Therefore, outcome variables were grouped in accordance with cognitive domains (e.g., executive function measures, memory measures), and a more stringent alpha level was applied (to interaction effects) to conserve statistical power (i.e., $p < .025$). Unlike repeated measures ANOVA, GLMMs do not rely on participants providing data at pre/post-intervention and follow-up. GLMMs use all data available at time intervals which

reduces the impact of participant attrition on statistical power. Moreover, GLMMs are rigorous against unequal groups (Krueger & Tian, 2004).

Each GLMM was first assessed for a statistically significant Group x Time interaction effect. A significant interaction effect indicated a differential rate of change in the outcome variable, between the control and intervention groups, across the time intervals. In accordance with the proposed hypotheses (see section 4.3), it was therefore predicted that there would be significant Group x Time interactions for all outcomes. Significant interaction effects were then examined for significant simple main effects of Time, for each group. A significant simple main effect of Time (per group) indicated that there was a change in outcome scores across the pre-intervention, post-intervention, and/or follow-up intervals. Significant simple main effects of Time were then examined for significant pairwise contrasts between time intervals, for each group. Statistically significant pairwise contrasts indicated a group's outcome scores had changed between time intervals. These pairwise contrasts were used to determine which groups demonstrated significant improvements on outcome variables.

Statistically significant simple main effects of Group were not of interest for this study. Significant simple main effects of Group indicate a significant difference between group outcome scores at either pre-intervention, post-intervention or follow-up time intervals. However, this study investigated whether there was a significantly different degree of change (over time) on outcome variables, between groups. Therefore, pre-intervention, post-intervention, or follow-up group differences provided no statistical evidence to support the effect of interventions (or no effect of the control group) on outcome variables.

4.4.1.1 Assumption testing. Similar to repeated measures ANOVA, three statistical assumptions pertain to GLMMs: normality, homogeneity of variance, and sphericity (Field, 2013). Each assumption was tested individually, per outcome variable. Normality refers to the distribution of scores on outcome variables demonstrating a relatively symmetrical inverted U-shape distribution, with most participant scores grouped in the center and less scores at either end of the distribution. Normality was assessed using the Shapiro-Wilk and skewness/kurtosis

statistics (Tabachnick & Fidell, 2013). A non-significant ($p > .05$) Shapiro-Wilk statistic and skewness/kurtosis statistics within ± 1.96, suggested that scores were normally distributed. Homogeneity of variance assumes that each group's scores are homogeneous (equal) in their variability (Field, 2013). Homogeneity of variance was assessed using the F_{max} method, where the largest sample variance was divided by the smallest sample variance. Largest and smallest sample variances were calculated by squaring the largest standard deviation and then squaring the smallest standard deviation. Tabachnick and Fidell (2013) recommend that homogeneity of variance can be assumed if F_{max} is less than 10. Lastly, the assumption of sphericity was assessed using Mauchly's Test of Sphericity. Sphericity assumes that the variances between the differences of outcome scores, at any two time intervals (e.g., pre to post, pre to follow-up, or post to follow-up), are approximately equal (Field, 2013). A non-significant ($p > .05$) Mauchly's result indicated that sphericity was met.

4.4.1.2 Power analysis and sample size. The sample for this study was determined during Study 1 (see Chapter 2.2.2.1). But for ease of exposition, an a priori power analysis was calculated using G*Power 3 (Faul et al., 2007). Power analysis was computed for an analysis of covariance (ANCOVA) as there is currently no statistical software available to determine an a priori sample size for GLMMs. To detect a moderate effect (power = .80 and $\alpha = .05$), 54 participants were required for analysis. To reduce the impact of potential participant attrition on statistical power, 90 participants (15 per group) were targeted for recruitment.

4.4.1.3 Effect size calculation. Effect sizes (Hedge's *g*) were calculated using the change score method, described in section 3.6.1.

4.5 Results

4.5.1 Preliminary Analyses

4.5.1.1 Missing data. No data was missing at pre-intervention. At post-intervention, however, one participant's data was missing for the depression subscale of the DASS-21 (DASS-D) and the PDQ-39, and five participants' data were missing for the SOC. This missing data equates to 6.7% of the DASS-D and the PDQ-39, and

33.5% of the SOC at post-intervention. Missing values analysis was conducted and Little's Missing Completely at Random (MCAR) test showed data missing at post-intervention was not systematically linked to included variables, χ^2 (27) = 23.80, p = .64. At follow-up assessments, seven participants' data were missing for the DASS-D and PDQ-39, and four participants' data were missing for the SOC. In addition, four participants withdrew from the study before follow-up assessments, providing no data across all outcomes. This missing data equates to 26.8% of the SOC and 46.9% of the DASS-D and PDQ-39. Little's MCAR test showed data missing at follow-up was not systematically linked to included variables, χ^2 (27) = 40.34, p = .05. Reasons for missing data included participants' failing to return completed questionnaires (despite follow up contact), and software malfunction with the CANTAB^{TM} program. Given that GLMMs account for missing data by using all data available at each time interval and that missing data analyses were not statistically significant, no data transformation or replacement technique was used prior to analysis (Krueger & Tian, 2004). Means and standard deviations calculated in the GLMMs at post-intervention and follow-up were therefore slightly adjusted by each model and do not reflect the raw data at those time points.

4.5.1.2 Participant flow. A total of 70 participants completed pre-intervention neuropsychological assessments, and 42 participants met inclusion criteria for this RCT. Participants were excluded for two reasons: (1) demonstrating cognitive functioning above MDS Task Force Level II criteria for PD-MCI (N = 25) and (2) severe cognitive impairment (N = 3). The researcher determined severe cognitive impairment as meeting MDS criteria, but demonstrating cognitive deficits that would have restricted a participant's ability to complete the cognitive training intervention. The 42 participants who completed the study were randomly allocated to an intervention group or the control group, resulting in 7 participants per group (see Figure 11). All participants completed their allocated interventions and post-intervention neuropsychological assessments. However, 4 participants (9.5%) did not complete follow-up assessments. Reasons for this attrition included an inability to travel due to disease progression (N = 2) and a lack of time to complete the follow-up assessment (N = 2).

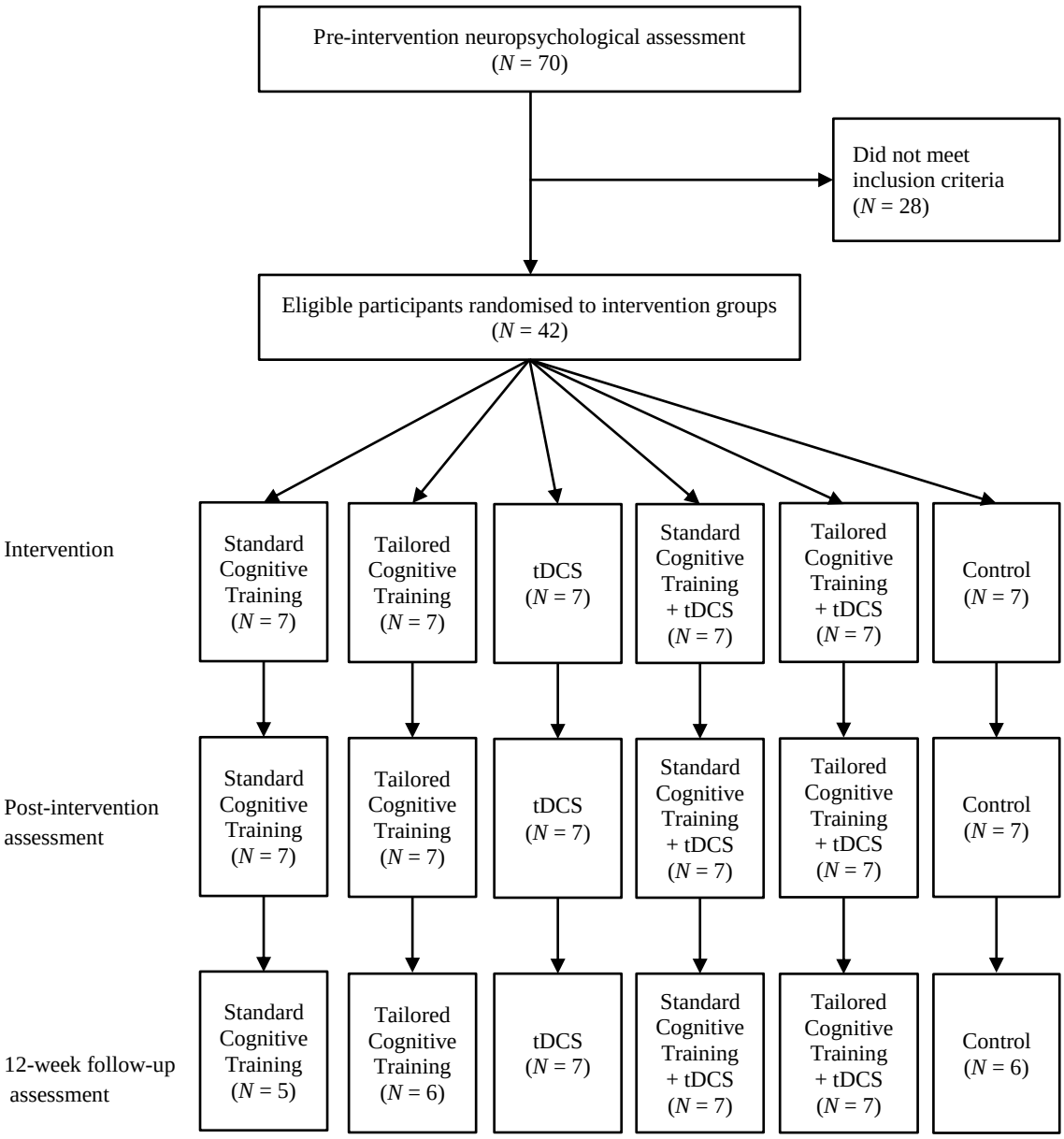

Figure 11. Flow Diagram of Participant Allocation

4.5.1.3 Statistical power. To provide sufficient power (.80, α = .05), this study required 54 participants (9 per group). However, only 42 participants (7 per group) met the inclusion criteria. This study was somewhat underpowered and the results should be interpreted as preliminary findings.

4.5.1.4 Demographic statistics. Table 6 provides demographic results for participants in the Standard Cognitive Training, Tailored Cognitive Training, tDCS,

Standard Cognitive Training + tDCS, Tailored Cognitive Training + tDCS, and Control groups.

Table 7

Demographic information for the intervention and control groups

	Standard CT		Tailored CT		tDCS	
Outcome	*M*	*SD*	*M*	*SD*	*M*	*SD*
Gender (% ♀)	43% (*N* = 3)		57% (*N* = 4)		71% (*N* = 5)	
Age^{++}	68.14	8.69	65.57	5.20	72	6.45
Education^{++}	13.57	2.64	12.21	2.83	13.57	3.69
Premorbid IQ	103.29	6.96	107.21	12	108.21	5.83
Disease Duration^{++}	5.29	4.23	5.79	4.97	5.50	5.66
LED	295	313.40	383	178.62	573.29	586.25
DASS-D	2.29	2.56	1.29	1.50	3	2
	Standard CT + tDCS		Tailored CT + tDCS		Control	
Outcome	*M*	*SD*	*M*	*SD*	*M*	*SD*
Gender (% ♀)	71% (*N* = 5)		71% (*N* = 5)		57% (*N* = 4)	
Age^{++}	63.57	15.68	67.43	6.37	72.29	6.21
Education^{++}	15.50	3.35	15.86	1.35	11.71	2.98
Premorbid IQ	111.96	4.37	111.08	3.59	103.64	7.53
Disease Duration^{++}	6.79	4.60	4.43	2.70	5.36	4.14
LED	350.71	322.37	464.29	358.78	292.88	274.51
DASS-D	3	5.07	3.29	4.11	2.71	3.15

Note. ♀ = male gender; $^{++}$ = years; CT = cognitive training; *M* = mean; *SD* = standard deviation; IQ = intelligence quotient; LED = levodopa equivalent dose; DASS-D = depression subscale of the Depression, Anxiety, and Stress Scale.

4.5.1.5 Pre-intervention correlations and covariate variables. Bivariate correlations were conducted to determine whether age, gender, years of education, premorbid IQ, disease duration, LED, and depression significantly correlated with outcome variables at pre-intervention. Age significantly correlated with the HVLT (r = -.43, p = .004), MMSE (r = -.43, p = .005), and PD-CRS (r = -.37, p = .018), and so was included as a covariate for these outcomes. Gender significantly correlated

with the Stroop test (r = .35, p = .025), and so was included as a covariate for this outcome. Years of education significantly correlated with Similarities (r = .31, p = .043) and MMSE (r = .34, p = .026), and so was included as covariate for these outcomes. Premorbid IQ significantly correlated with Similarities (r = .44, p = .003), JLO (r = .33, p = .034) and MMSE (r = .38, p = .014), and so was included as a covariate for these outcomes. Disease duration significantly correlated with the HVOT (r = -.32, p = .044) and was included as a covariate for this outcome. LED significantly correlated with Similarities (r = .33, p = .032) and was included as a covariate for this outcome. Lastly, depression significantly correlated with Similarities (r = -.39, p = .011) and the PDQ-39 (r = .59, p < .001), and so was included as a covariate for these outcomes. No other significant correlations were found.

4.5.2 Generalised Linear Mixed Models

4.5.2.1 Assumption testing. No outcomes violated the assumption of sphericity. The assumption of normality was violated for five outcomes (MMSE, HVLT, JLO, BNT, and LNS) according to Shapiro-Wilk (p < .05; see Appendix D). However, three outcomes (MMSE, HVLT, and JLO) showed skewness/kurtosis statistics within the acceptable range (± 1.96), suggesting these variables were normally distributed. Two outcomes (BNT and LNS) showed large kurtosis statistics (BNT = 3.02; LNS = 2.83), suggesting these variables were not normally distributed. Eight outcomes (MMSE, PD-CRS, JLO, BNT, Paragraph recall, LNS, COWAT, and UPDRS-II) violated the homogeneity of variance assumption, with F_{max} values greater than 10. GLMMs are, however, robust against violations of normality and homogeneity of variance when group sizes are relatively equal (Krueger & Tian, 2004). Therefore, no data transformation technique was used to account for assumption violations.

4.5.2.2 Hypothesis testing. To address each hypothesis, outcomes were examined for statistically significant Time x Group interaction effects, simple main effects of Time (per group), and group pairwise contrasts. Raw outcome scores for each group at pre-intervention, post-intervention, and follow-up are in Appendices E,

F, and G. Effect sizes in accordance with each hypothesis are reported in Appendix H. To ease exposition, each hypothesis is summarised here:

H1: Compared to participants in the Control group, participants in the Standard Cognitive Training, Tailored Cognitive Training, tDCS, Standard Cognitive Training + tDCS, and Tailored Cognitive Training + tDCS groups will demonstrate statistically significantly larger improvements for all outcomes across all assessment intervals.

H2: Compared to participants in the Standard Cognitive Training group, participants in the Tailored Cognitive Training, tDCS, Standard Cognitive Training + tDCS, and Tailored Cognitive Training + tDCS groups will demonstrate statistically significantly larger improvements for all outcomes across all assessment intervals.

H3: Compared to participants in the Tailored Cognitive Training group, participants in the tDCS, Standard Cognitive Training + tDCS, and Tailored Cognitive Training + tDCS groups will demonstrate statistically significantly larger improvements for all outcomes across all assessment intervals.

H4: Compared to participants in the tDCS group, participants in the Standard Cognitive Training + tDCS and Tailored Cognitive Training + tDCS groups will demonstrate statistically significantly larger improvements for all outcomes across all assessment intervals.

H5: Compared to participants in the Standard Cognitive Training + tDCS group, participants in the Tailored Cognitive Training + tDCS group will demonstrate statistically significantly larger improvements for all outcomes across all assessment intervals.

4.5.2.2.1 Executive function. For Stockings of Cambridge (SOC), H1, H2, H3, and H4 were partially supported. H5 was not supported. Figure 12 shows groups with statistically significant improvement in SOC scores and the control group.

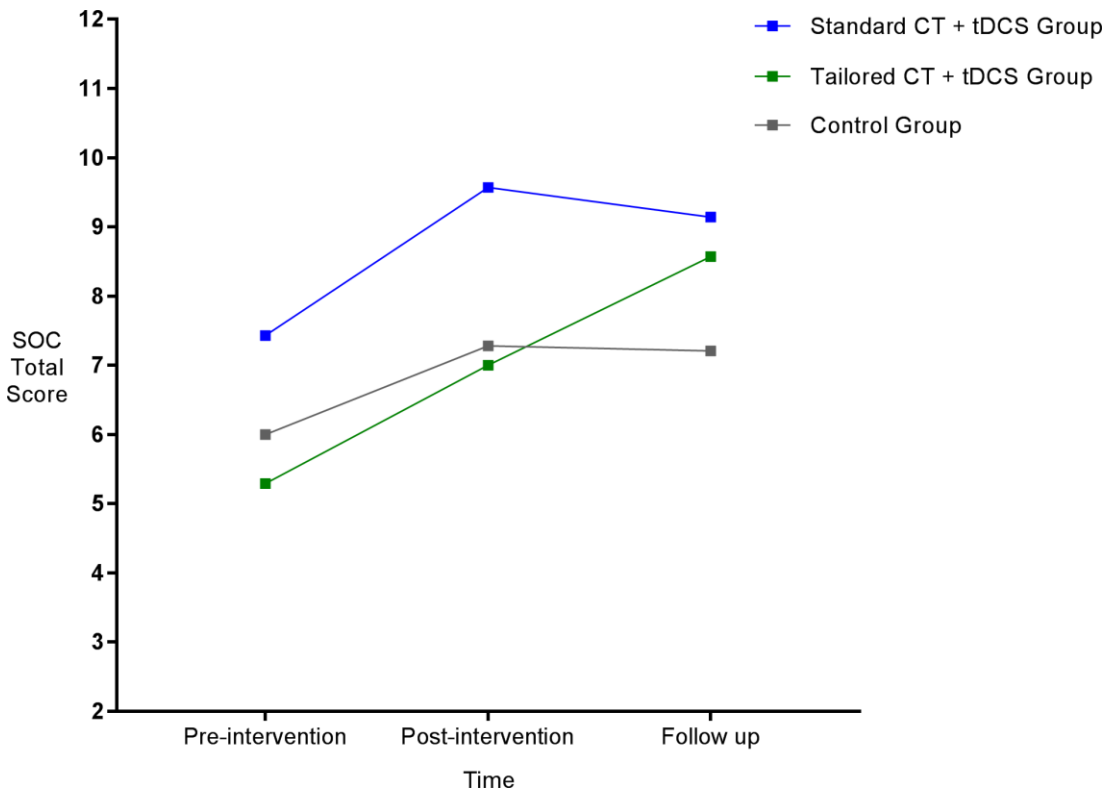

Figure 12. Trajectory of change in SOC total scores for intervention groups with statistically significant improvement and for the control group. *Note: 95% confidence interval bars have been omitted from each data point to ease interpretation of the figure.*

A significant interaction effect was observed for SOC, indicating a differential rate of change in executive function between groups, F (10, 95) = 3.82, p < .001. A significant simple main effect of Time was observed for the Standard Cognitive Training + tDCS group, F (2, 95) = 10.73, p < .001. Pairwise contrasts revealed significant improvement in executive function from pre-intervention to post-intervention, t (95) = 2.15, p < .001, g = .41, and from pre-intervention to follow-up, t (95) = 1.71, p = .024, g = .23. A significant simple main effect of Time was observed for the Tailored Cognitive Training + tDCS group, F (2, 95) = 12.00, p < .001. Pairwise contrasts revealed significant improvement in executive function from pre-intervention to post-intervention, t (95) = 1.71, p = .024, g = .19, and from pre-intervention to follow-up, t (95) = 3.29, p < .001, g = .92. No significant simple main effects of Time were observed for the Standard Cognitive Training group (F [2,

95] = 2.00, p = .14), Tailored Cognitive Training group (F [2, 93] = .96, p = .39), tDCS group (F [2, 93] = 2.38, p = .10), or Control group (F [2, 93] = 3.15, p = .05).

For the Controlled Oral Word Association Test (COWAT), the interaction effect was not significant and indicated no differential rate of change between groups, F (10, 104) = 1.65, p = .10. Therefore, no hypotheses were supported for this outcome.

4.5.2.2.2 Attention/working memory. For the Stroop test, H1, H2, and H3 were partially supported. H4 and H5 were not supported. Figure 13 shows groups with statistically significant improvement in Stroop test scores.

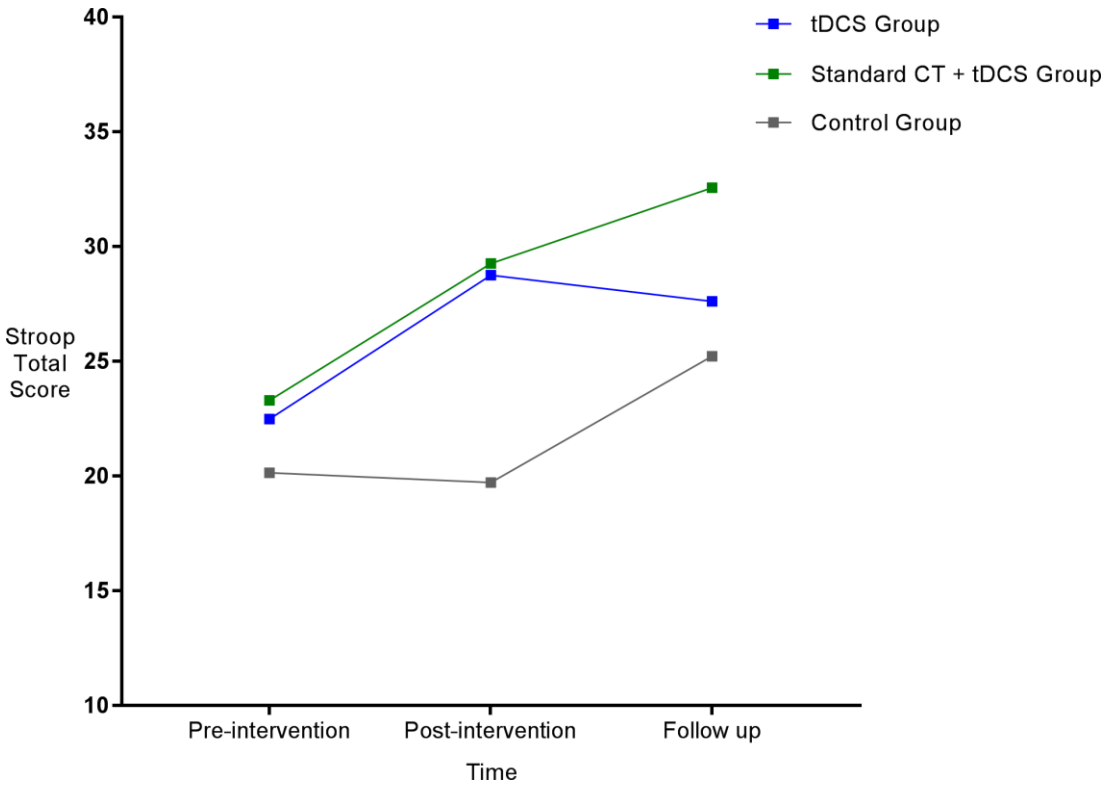

Figure 13. Trajectory of change in Stroop total scores for intervention groups with statistically significant improvement and for the control group.

A significant interaction effect was observed for the Stroop test, indicating a differential rate of change in attention/working memory between groups, F (10, 103)

= 2.91, p = .003. A significant simple main effect of Time was observed for the tDCS group, F (2, 103) = 4.06, p = .020. Pairwise contrasts revealed significant improvement in attention/working memory from pre-intervention to post-intervention, t (103) = 6.29, p = .039, g = .65, and from pre-intervention to follow-up, t (103) = 5.14, p = .018, g = .01. A significant simple main effect of Time was observed for the Standard Cognitive Training + tDCS group, F (2, 103) = 35.05, p < .001. Pairwise contrasts revealed significant improvement in attention/working memory from pre-intervention to post-intervention, t (103) = 6.00, p = .028, g = .60 and from pre-intervention to follow-up, t (103) = 9.29, p < .001, g = .24. No significant simple main effects of Time were observed for the Standard Cognitive Training group (F [2, 103] = 1.61, p = .20), Tailored Cognitive Training group (F [2, 103] = 1.08, p = .34), Tailored Cognitive Training + tDCS group (F [2, 103] = 1.45, p = .24), and Control group (F [2, 103] = .56, p = .57).

For Letter-Number Sequencing (LNS), H1, H2, H4, and H5 were partially supported. H3 was not supported. A significant interaction effect was observed for LNS, indicating a differential rate of change in attention/working memory between groups, F (10, 95) = 4.53, p < .001. A significant simple main effect of time was observed for the Standard Cognitive Training group, F (2, 95) = 16.41, p < .001. However, pairwise contrasts revealed no significant differences from pre-intervention to post-intervention, or to follow-up. A significant simple main effect of time was observed for the Tailored Cognitive Training group, F (2, 95) = 6.62, p = .002. Pairwise contrasts revealed a significant improvement in attention/working memory from pre-intervention to follow-up, t (95) = 2.42, p = .001, g = .34. No improvements were observed from pre-intervention to post-intervention. A significant simple main effect of time was observed for the Tailored Cognitive Training + tDCS group, F (2, 95) = 5.11, p = .008. Pairwise contrasts revealed a significant improvement in attention/working memory from pre-intervention to follow-up, t (95) = 1.61, p = .030, g = .22. No improvements were observed from pre-intervention to post-intervention. No significant simple main effects of Time were observed for the tDCS group (F [2, 95] = 1.83, p = .17), Standard Cognitive Training + tDCS group (F [2, 95] = .09, p = .91), and Control group (F [2, 95] = .58, p = .56). Figure 14 shows groups with statistically significant improvement in LNS scores.

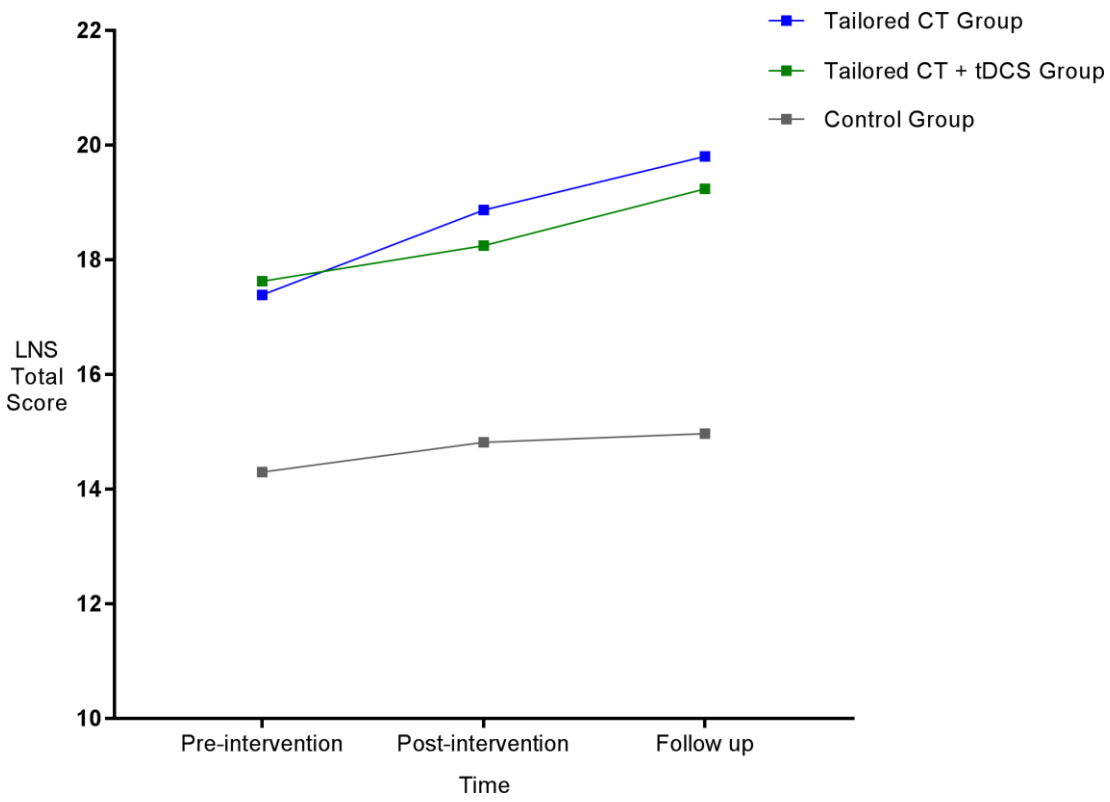

Figure 14. Trajectory of change in LNS total scores for intervention groups with statistically significant improvement and for the control group.

4.5.2.2.3 Memory. For Paragraph recall, H1, H3, and H5 were partially supported. H2 and H4 were not supported. A significant interaction effect was observed for Paragraph recall, indicating a differential rate of change in memory between groups, F (10, 104) = 2.51, p = .010. A significant simple main effect of Time was observed for the Standard Cognitive Training group, F (2, 104) = 5.24, p = .007. Pairwise contrasts revealed a significant improvement in memory from pre-intervention to follow-up, t (104) = 2.09, p = .002, g = 1.30. No improvements were observed from pre-intervention to post-intervention. A significant simple main effect of Time was observed for the tDCS group, F (2, 104) = 17.82, p < .001. Pairwise contrasts revealed a significant improvement in memory from pre-intervention to post-intervention, t (104) = 2.29, p < .001, g = 1.11. No improvements were observed from pre-intervention to follow-up. A significant simple main effect of Time was observed for the Tailored Cognitive Training + tDCS group, F (2, 104) =

12.09, $p < .001$. Pairwise contrasts revealed a significant improvement in memory from pre-intervention to post-intervention, t (104) = 2.50, $p < .001$, g = 1.36, and from pre-intervention to follow-up, t (104) = 3.21, p = .002, g = 1.75. No significant simple main effects of Time were observed for the Tailored Cognitive Training group (F [2, 104] = 2.87, p = .06), Standard Cognitive Training + tDCS group (F [2, 104] = 2.86, p = .06), and Control group (F [2, 104] = .97, p = .38). Figure 15 shows groups with statistically significant improvement in Paragraph recall scores.

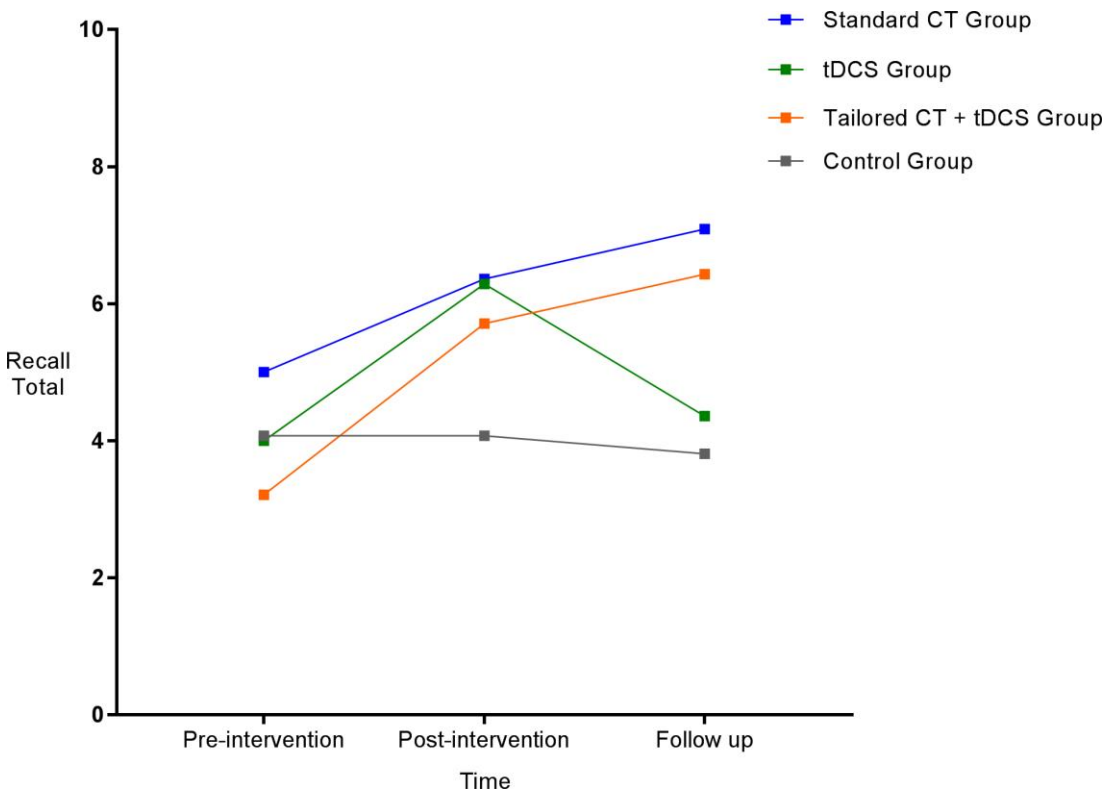

Figure 15. Trajectory of change in Paragraph recall total scores for intervention groups with statistically significant improvement and for the control group.

For Hopkins Verbal Learning Test (HVLT), the interaction effect was not significant and indicated no differential rate of change between groups, F (10, 103) = .87, p = .56. Therefore, no hypotheses were supported for this outcome.

4.5.2.2.4 Language. For Similarities, H1, H2, H3, and H4 were partially supported. H5 was not supported. A significant interaction effect was observed for Similarities, indicating a differential rate of change in language between groups, F

(10, 92) = 3.25, p = .001. A significant simple main effect of Time was observed for the Standard Cognitive Training + tDCS group, F (2, 92) = 5.23, p = .007. Pairwise contrasts revealed a significant improvement in language from pre-intervention to post-intervention, t (92) = 1.92, p = .008, g = .59. But no improvements were observed from pre-intervention to follow-up. A significant simple main effect of Time was observed for the Tailored Cognitive Training + tDCS group, F (2, 92) = 17.43, p < .001. Pairwise contrasts revealed a significant improvement in language from pre-intervention to post-intervention, t (92) = 3.13, p < .001, g = 1.06. But no improvements were observed from pre-intervention to follow-up. No significant simple main effects of Time were observed for the Standard Cognitive Training group (F [2, 92] = 1.55, p = .22), Tailored Cognitive Training group (F [2, 92] = .29, p = .75), tDCS group (F [2, 92] = 1.41, p = .25), and Control group (F [2, 92] = 1.78, p = .18). Figure 16 shows groups with statistically significant improvement in Similarities scores.

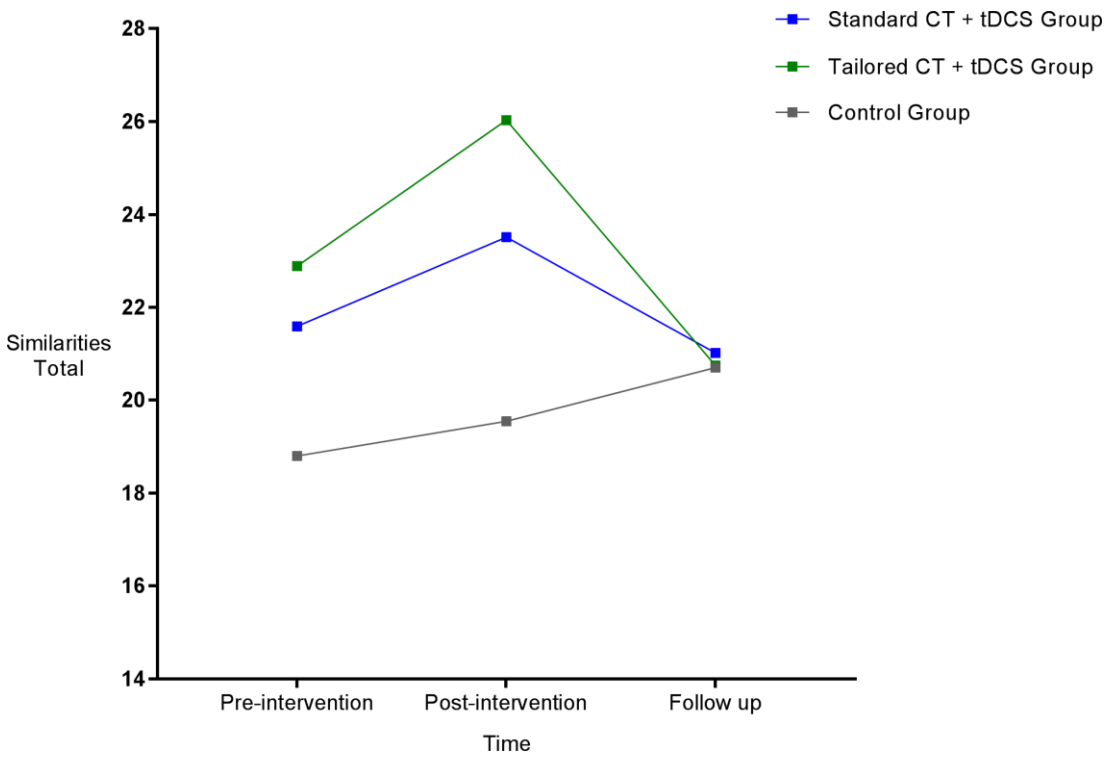

Figure 16. Trajectory of change in Similarities total scores for intervention groups with statistically significant improvement and for the control group.

For the Boston Naming Test (BNT), the interaction effect was not significant and indicated no differential rate of change between groups, F (10, 104) = 1.24, p = .28. Therefore, no hypotheses were supported for this outcome.

4.5.2.2.4 Visuospatial abilities. A significant interaction effect was observed for Judgement of Line Orientation (JLO), indicating a differential rate of change in visuospatial abilities between groups, F (10, 103) = 3.76, $p < .001$. A significant simple main effect of Time was observed for the Standard Cognitive Training group, F (2, 103) = 6.57, $p = .002$. However, pairwise contrasts revealed a significant decline in visuospatial abilities from pre-intervention to follow-up, t (103) = 5.00, $p = .004$, $g = -.32$. No improvements were observed from pre-intervention to post-intervention. A significant simple main effect of Time was observed for the Control group, F (2, 103) = 7.46, $p = .001$. However, pairwise contrasts revealed no significant differences from pre-intervention to post-intervention, or to follow-up. No significant simple main effects of Time were observed for the Tailored Cognitive Training group (F [2, 103] = 3.19, $p = .05$), tDCS group (F [2, 103] = 2.85, $p = .06$), Standard Cognitive Training + tDCS group (F [2, 103] = 1.87, $p = .16$), and Tailored Cognitive Training + tDCS group (F [2, 103] = .21, $p = .81$). These results indicate that no hypotheses were supported for this outcome.

For Hooper's Visual Organisation Test (HVOT), the interaction effect was not significant and indicated no differential rate of change between groups, F (10, 99) = 1.18, $p = .32$. Therefore, no hypotheses were supported for this outcome.

4.5.2.2.5 Global cognition. Interaction effects were not significant for the Mini Mental State Examination (MMSE), F (10, 101) = 1.74, $p = .08$, and the Parkinson's Disease-Cognitive Rating Scale (PD-CRS), F (10, 103) = 2.06, $p = .035$ (using a Bonferroni adjusted alpha level, $p = .025$). These results indicate no differential rate of change in global cognition between groups, and so no hypotheses were supported for these outcomes.

4.5.2.2.6 Activities of daily living. For the Unified Parkinson's Disease Rating Scale – section II (UPDRS-II), H1, H3, and H4 were partially supported. H2 and H5 were not supported. Figure 17 shows groups with statistically significant improvement in UPDRS-II scores.

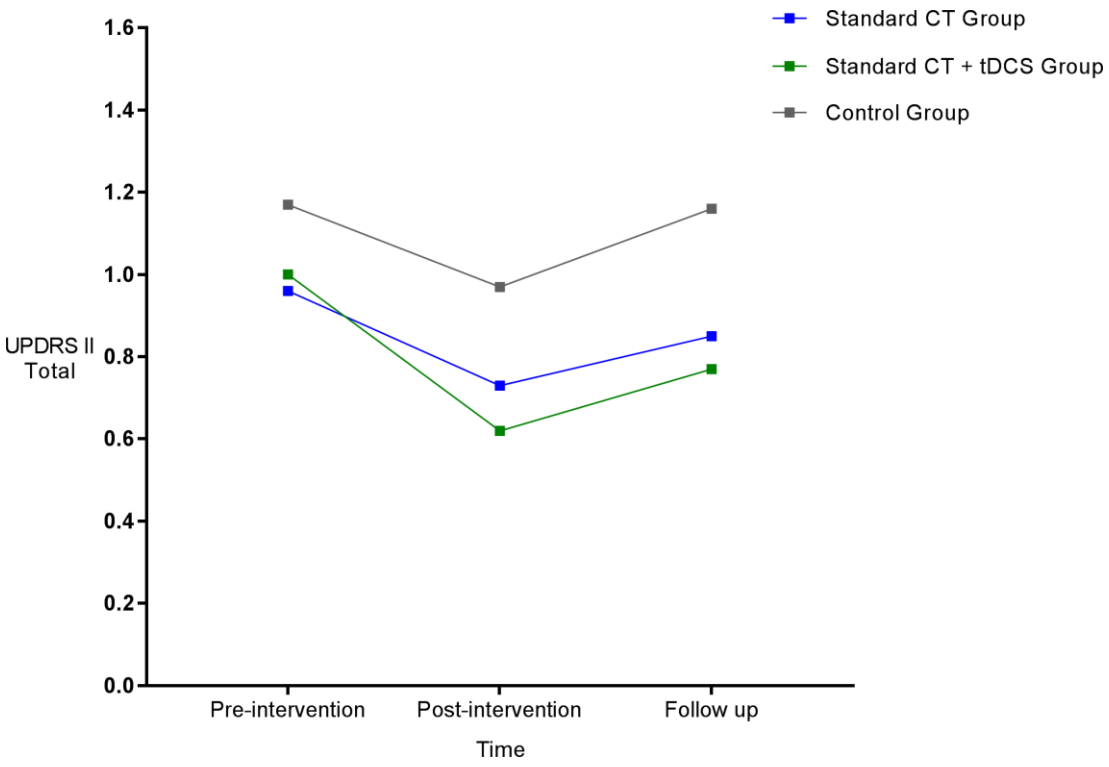

Figure 17. Trajectory of change in UPDRS-II total scores for intervention groups with statistically significant improvement and for the control group.

A significant interaction effect was observed for the UPDRS-II, indicating a differential rate of change in activities of daily living between groups, F (10, 104) = 1.96, p = .045. A significant simple main effect of Time was observed for the Standard Cognitive Training group, F (2, 104) = 11.29, p < .001. Pairwise contrasts revealed a significant improvement in activities of daily living from pre-intervention to post-intervention, t (104) = -.23, p < .001, g = .33. No improvements were observed from pre-intervention to follow-up. A significant simple main effect of Time was observed for the Standard Cognitive Training + tDCS group, F (2, 104) = 3.40, p = .037. Pairwise contrasts revealed a significant improvement in activities of daily living from pre-intervention to post-intervention, t (104) = -.38, p = .014, g = .55. No improvements were observed from pre-intervention to follow-up. A significant simple main effect of Time was observed for the Tailored Cognitive Training + tDCS group, F (2, 104) = 16.96, p < .001. However, pairwise contrasts revealed no significant differences from pre-intervention to post-intervention, or to follow-up. No significant simple main effects of Time were observed for the Tailored

Cognitive Training group (F [2, 104] = .48, p = .62), tDCS group (F [2, 104] = 2.54, p = .08), and Control group (F [2, 104] = .57, p = .57).

4.5.2.2.7 Quality of life. For the Parkinson's Disease Questionnaire-39 (PDQ-39), H1 was partially supported. H2, H3, H4, and H5 were not supported. Figure 18 shows groups with statistically significant improvement in PDQ-39 scores.

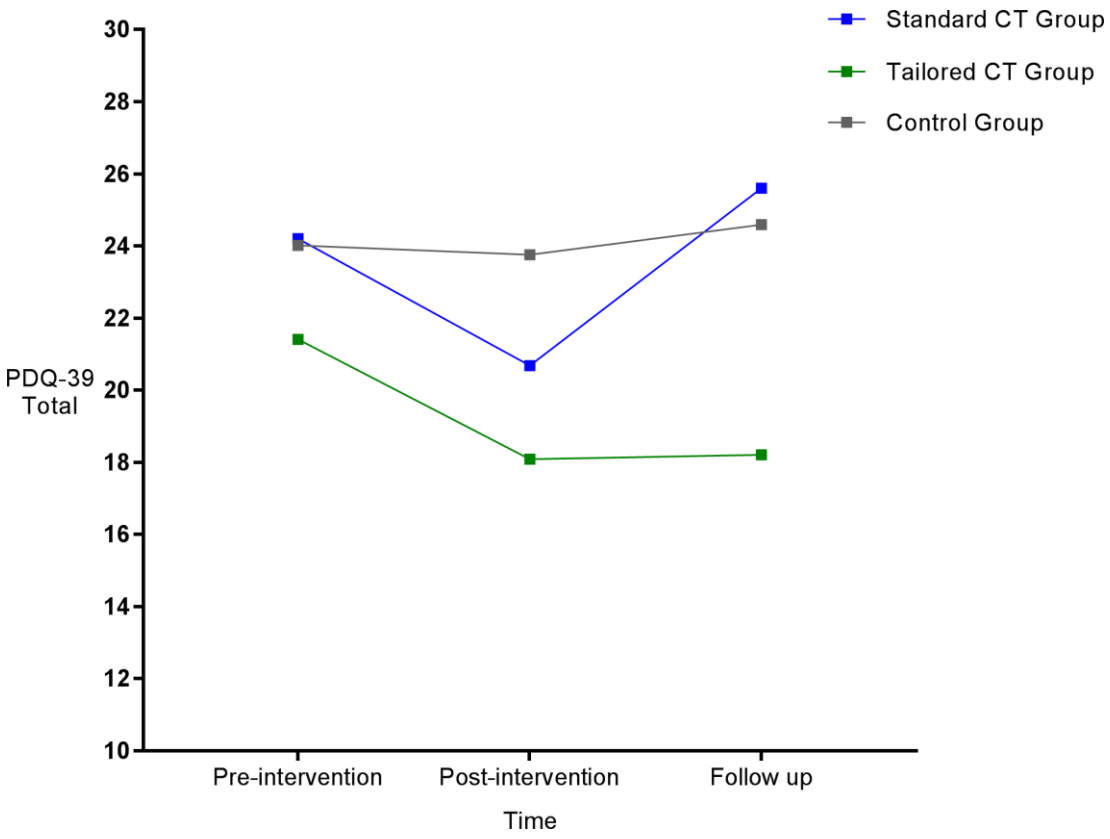

Figure 18. Trajectory of change in PDQ-39 total scores for intervention groups with statistically significant improvement and for the control group.

A significant interaction effect was observed for the PDQ-39, indicating a differential rate of change in quality of life between groups, F (10, 95) = 2.96, p = .003. A significant simple main effect of Time was observed for the Standard Cognitive Training group, F (2, 95) = 7.21, p = .001. Pairwise contrasts revealed a significant improvement in quality of life from pre-intervention to post-intervention, t (95) = -3.52, p = .003, g = .24. No improvements were observed from pre-intervention to follow-up. A significant simple main effect of Time was observed for the Tailored Cognitive Training group, F (2, 95) = 12.48, p < .001. Pairwise contrasts

revealed a significant improvement in quality of life from pre-intervention to post-intervention, t (95) = -3.32, p = .016, g = .26, and from pre-intervention to follow-up, t (95) = -3.20, p = .017, g = .12. A significant simple main effect of Time was observed for the Tailored Cognitive Training + tDCS group, F (2, 95) = 3.85, p = .025. However, pairwise contrasts revealed no significant differences from pre-intervention to post-intervention, or to follow-up. No significant simple main effects of Time were observed for the tDCS group (F [2, 95] = .63, p = .54), Standard Cognitive Training + tDCS group (F [2, 95] = 1.73, p = .18) and Control group (F [2, 95] = .30, p = .75).

4.6 Discussion

This study was the first randomised controlled trial of standard cognitive training, tailored cognitive training, tDCS, standard cognitive training + tDCS, and tailored cognitive training + tDCS for mild cognitive impairment in PD. In support of the therapeutic potential of these nonpharmacological interventions, differential rates of statistically significant improvements in cognition, activities of daily living, and quality of life were observed across various intervention groups. The control group did not improve on outcome measures.

4.6.1 Main Findings and Implications

Standard cognitive training involves the repetitive presentation of external stimuli to induce synaptic plasticity by altering neural connectivity at a cellular level (Kim & Kim, 2014). Within Kim and Kim's (2014) theoretical framework, standard cognitive training is a *stimulation-focussed* intervention that broadly enhances cognitive function by changing existing neural connections in the brain. In this study, the Standard Cognitive Training group improved on memory, but no improvements were found for any other cognitive domains. Improvements were observed on the Paragraph recall test (g = .62) from pre-intervention to post-intervention, but improvements were not maintained at follow-up neuropsychological assessments. These results are supported by previous studies, with standard cognitive training improving memory in PD (París et al., 2011; Pena et al., 2014; Petrelli et al., 2014). Two previous studies, however, reported improvement in visuospatial related

memory abilities (París et al., 2011; Pena et al., 2014) and no improvement on paragraph recall tasks that primarily assess logical memory. This discrepancy between studies may be explained by the 'dual syndrome hypothesis' (Nombela et al., 2014). The dual syndrome hypothesis suggests that distinct genetic variations are associated with memory (APOE allelic) and visuospatial (MAPT haplotype) deficits in PD (Kehagia et al., 2010). If the majority of participants in the previous studies had the MAPT haplotype genetic abnormality (associated with visuospatial impairment), and participants in the current study had the APOE allelic abnormality (associated with memory impairment), then standard cognitive training would likely produce stimulation-focussed effects to improve abilities associated with specific cognitive deficits and their corresponding genetic abnormality. Functional magnetic resonance imaging (fMRI) was beyond the scope of the present study, but future clinical trials need to integrate cognitive training with neuroimaging to assist with understanding the neurobiological processes involved during these interventions.

For the Standard Cognitive Training group, activities of daily living (g = .33) and quality of life (g = .24) also improved from pre-intervention to post-intervention, but improvements were not maintained at follow-up assessments. One standard cognitive training study has reported improvements in activities of daily living (Pompeu et al., 2012), but the current study is the first to report significant improvements in quality of life in PD from pre to post-intervention. París et al. (2011) used the same computer-based cognitive training program (Smartbrain Pro™) and the same quality of life outcome measure (PDQ-39), but their participants did not improve on quality of life. Half of the participants in Paris et al.'s (2011) cognitive training group were, however, classified as having normal cognition. Participants with normal cognitive functioning may have experienced a ceiling effect, which limits the therapeutic potential of cognitive training and associated improvements in quality of life. Despite limited evidence to support the findings of the current study, quality of life and activities of daily living are frequently impaired in PD and are associated with cognitive decline (Klepac et al., 2008; Lawrence et al., 2014; Muslimović et al., 2008). The current results indicate that standard cognitive training may provide improvements in activities of daily living and quality of life for people with PD-MCI, and future cognitive training studies need to include these measures as primary outcomes.

Building upon standard cognitive training, tailored cognitive training also uses external stimuli to alter neural connectivity and target specific cognitive impairments, to compensate for deficits in these domains. Theoretically, tailored cognitive training is a *stimulation* and *compensation-focussed* intervention aimed at improving specific cognitive functions that have been impacted by neural degeneration (Kim & Kim, 2014). In the present study, the Tailored Cognitive Training group improved on attention/working memory (measured by LNS, g = .34) from pre-intervention to follow-up, but no improvements were observed at post-intervention assessments. That is, no immediate post-intervention improvement was evident. The improvement in attention/working memory was delayed and only presented 12-weeks post-intervention cessation. One other tailored cognitive training study has reported immediate post-intervention 'attentional improvements', evidenced by increased neural resting state (measured by fMRI) activity in the superior parietal and prefrontal dorsolateral cortices following training (Cerasa et al., 2014). In the current study, however, improvements in attention/working memory were not observed until the 12-week follow-up assessment. Methodological differences may account for the discrepancy between results. Compared to the current study, Cerasa et al. (2014) administered 12-sessions of tailored cognitive training in a supervised group setting. Group-based cognitive training has shown greater efficacy than in-home cognitive training in healthy-older adults (Lampit et al., 2014). Group-based training may provide additional benefits including trainer supervision, encouragement in performance, and social interaction among participants (Lampit et al., 2014). Participants may therefore adhere to and benefit from a group-based intervention to a greater extent. In addition, several participants in the current study's tailored cognitive training group provided feedback (albeit anecdotally) suggesting that the training was, at times, monotonous and too repetitive. Compared to the standard cognitive training format, those randomised to tailored cognitive training only completed activities targeting their impaired cognitive domains (i.e., a less diverse and engaging cognitive training program). These methodological parameters may be associated with the lack of post-intervention improvement in the current study. Nonetheless, the Tailored Cognitive Training Group did improve on attention/working memory at the follow-up

assessment, which provides some preliminary evidence to support future tailored cognitive training studies.

The Tailored Cognitive Training group also improved on quality of life from pre-intervention to post-intervention (g = .26), and improvements were maintained at follow-up assessment (g = .12). This is the first study to report improvements in quality of life following tailored cognitive training in people with PD or PD-MCI. Despite limited evidence in PD, a Cochrane review of cognitive training for people with mild to moderate dementia reported positive effects of cognitive training for quality of life (Woods, Aguirre, Spector, & Orrell, 2012). From the 15 RCTs included in the review, participants with dementia demonstrated improvements in self-reported quality life (as well as cognitive function) following cognitive training (Woods et al., 2012). An earlier study of cognitive training in dementia reported improvements in quality of life were mediated by improvements in cognition (Woods, Thorgrimsen, Spector, Royan, & Orrell, 2006). This result suggests that the beneficial effects of cognitive training for quality of life may be reliant upon cognitive improvement during training, and quality of life is less likely to improve if no cognitive benefits are observed. It is currently not known whether there is individual or multiple neurobiological mechanisms associated with improved quality of life following cognitive training. However, the positive results in the present study and those reported in dementia indicate that future studies need to explore the potential of tailored cognitive training for improving quality of life in PD-MCI.

tDCS modulates neuronal activity by delivering low intensity electrical currents to specific cortical regions (Creutzfeldt et al., 1962; Nardone et al., 2012). Several neuroimaging studies report increased activation of the prefrontal cortices when older adults complete tasks involving attention/working memory and/or executive skills (Spreng, Wojtowicz, & Grady, 2010). That is, older adults experience greater activation of frontal cortical networks during complex cognitive tasks to compensate for impaired performance in other cortical regions (Goh & Park, 2009). Within Kim and Kim's (2014) theoretical framework, anodal tDCS used in this study was a *compensation-focussed* intervention to improve cognitive impairments associated with compensatory activation of the left DLPFC in people with PD-MCI. The tDCS group improved on attention/working memory (Stroop test)

from pre-intervention to post-intervention (g = .65), and improvements were maintained at follow-up assessments (g = .01). To date, one tDCS study has reported significant improvement on attention/working memory in PD (Boggio et al., 2006) and two studies reported improvement on executive function (Doruk et al., 2014; Pereira et al., 2013). As described in section 3.8.2, however, recent tDCS (and cognitive training) studies have heterogeneously applied neuropsychological tests to the measurement of cognitive domains, which leads to variability in the reporting of intervention effects for improving cognitive functions.

In this study, the MDS Task Force criteria for PD-MCI was used to categorise neuropsychological tests (Litvan et al., 2012). The MDS criteria suggest using the Stroop test to measure attention/working memory and in the current study, the tDCS group demonstrated significant improvements on this domain. However, the Stroop test's incongruent colour-word naming task (which was used in this study) primarily assesses an individual's ability to inhibit a prepotent word response (Fisk & Sharp, 2004). Inhibition has been proposed as an executive function ability (Fisk & Sharp, 2004; Miyake et al., 2000), which suggests that the tDCS group may have improved an executive function skill other than attention/working memory. Further discrepancies between test classifications are also highlighted when comparing the methods employed by Doruk et al. (2014) and the formal test classification methods recommended by Strauss et al. (2006) and the MDS criteria. Doruk et al. (2014) administered tDCS and reported improvement in 'executive abilities' as measured by the Trail Making Test-Part B (TMT-B). Strauss et al. (2006) and the MDS criteria classify the TMT-B as a measure of attention/working memory, which is consistent with Baddeley (2003) suggestion that the 'central executive' involves the use of attentional control and is one underlying component of the broader working memory domain. The method used to classify specific cognitive skills and neuropsychological tests within a cognitive domain, will therefore determine which domain is described as improved during a clinical trial. Despite the heterogeneous use of neuropsychological tests in PD, the results of this study suggest that tDCS can improve attention/working memory (or inhibition as an executive skill) in people with PD-MCI.

The tDCS group demonstrated significant improvements on memory (Paragraph recall, g = 1.11) from pre-intervention to post-intervention, but improvements were not maintained at follow-up assessments. The current study is the first to report memory improvement following tDCS in PD-MCI. Several studies in AD have reported improvements in memory following tDCS. Boggio et al. (2009) compared the effect of anodal tDCS over the left temporal cortex and left DLPFC, against sham tDCS in AD. Anodal stimulation over both cortical sites led to significant improvement in visual recognition memory immediately following stimulation, but no long-term effect was reported (Boggio et al., 2009). Ferrucci et al. (2008) compared anodal, cathodal, and sham tDCS applied over the temporoparietal areas in AD. Significant improvement in recognition memory was observed immediately following anodal tDCS (Ferrucci et al., 2008), without long-term improvements. In a follow up study, Boggio et al. (2012) reported improvement in visual recognition memory following anodal tDCS over the temporal cortex and effects were maintained one month post-stimulation. The results observed in AD provide empirical support for the positive effects demonstrated in the current study, suggesting that anodal tDCS over both temporal and dorsolateral cortices may induce compensatory activation of neural networks associated with improvements in memory for individuals with a neurodegenerative disorder (i.e., PD-MCI). As previously noted, participants in the current study may have had the APOE allelic genetic abnormality associated with memory deficits in the posterior cortex (Nombela et al., 2014). In accordance with the Scaffolding Theory of Ageing and Cognition (Goh & Park, 2009), impaired posterior cortical function may have resulted in compensatory activation of the prefrontal cortices (i.e., left DLPFC), to account for increased cognitive demand during complex tasks (i.e., neuropsychological assessments). Anodal tDCS therefore enhanced compensatory activation of the left DLPFC, leading to increased neural activity of frontal functions that were associated with improved memory performance in PD-MCI.

This study was the first controlled trial in PD or PD-MCI to combine standard cognitive training with tDCS. In accord with Kim and Kim's (2014) model, combining standard cognitive training with tDCS ensured participants in this group received a *stimulation* and *compensation-focussed* intervention. In the present study, the Standard Cognitive Training + tDCS group demonstrated significant

improvement on executive function (SOC, g = .41) and attention/working memory (Stroop test, g = .60) from pre-intervention to post-intervention, and improvements were maintained at follow-up assessment (SOC, g = .23; Stroop test, g = .24). A number of uncontrolled studies have combined standard cognitive training with noninvasive brain stimulation, but the results vary. In the only study of PD-MCI, Biundo et al. (2015) examined the effect of combining standard cognitive training with either real or sham tDCS. For participants in the real tDCS group, a significant decline in executive skills but significant improvements in attention and memory were observed (Biundo et al., 2015). Improvements were not maintained at 16-week follow up assessments and this study did not include a control group, which limits interpretation of the results. Two studies in AD paired repetitive transcranial magnetic stimulation (rTMS) with standard cognitive training and reported significant improvement in global cognition at an 18-week follow up assessment (Bentwich et al., 2011; Rabey et al., 2013). Although they are different methods of non-invasive stimulation, both anodal tDCS and high frequency rTMS increase cortical excitability to improve cognitive functioning in these neurodegenerative disorders (Nardone et al., 2012). According to Mowszowski et al. (2010), combining standard cognitive training with tDCS in the current study may have resulted in 'positive plasticity' to alleviate executive function and attention/working memory deficits in PD-MCI. Standard cognitive training may have stimulated and strengthen existing neural connections (i.e., synaptogenesis; Ponti et al., 2008), while tDCS provided compensatory activation of a cortical region (i.e., left DLPFC) associated with higher-order cognition (i.e., executive function and working memory). In combination, these nonpharmacological interventions produced beneficial effects on cognition for people with PD-MCI.

Among studies administering cognitive training or tDCS independent of one another, most report short-term cognitive improvement immediately following interventions (Boggio et al., 2006; Costa et al., 2014; París et al., 2011; Pereira et al., 2013), with one study reporting improvements were maintained up to 4-weeks post-tDCS (Doruk et al., 2014). Combining standard cognitive training and tDCS in the present study resulted in maintenance of executive function and attention/working memory improvements for 12-weeks post cessation of intervention. Pairing anodal tDCS applied to the left DLPFC with 12-sessions of standard cognitive training may

induce stimulation and compensation-focussed neuronal plasticity in people with PD-MCI, and lead to long-term improvements in cognition.

The Standard Cognitive Training + tDCS group improved on language (Similarities, g = .59) from pre-intervention to post-intervention, but improvements were not maintained at follow up assessment. This study is the first standard cognitive training and tDCS study to report language improvements in PD-MCI. This significant improvement in language abilities may be explained by the overlap between the language skills needed to complete the Similarities test (pre and post-intervention) and the language skills employed during the cognitive training program. When completing the language activities (Smartbrain Pro^{TM}), participants were required to finish sentences by selecting an appropriate word and determine the relationship between a group of words by applying a semantic category to those words. Successful completion of the Similarities test also involves application of semantic word categories to describe the most appropriate relationship between a set of words (Wechsler, 2008). Participants in the Standard Cognitive Training + tDCS group may have trained and improved language skills that were most beneficial for successful performance on the Similarities language test. As described in sections 3.2.1.3 and 3.2.2.3, however, very few cognitive training and no rTMS or tDCS studies have included a standardised measurement of language abilities, as language deficits are not typically associated with PD (Litvan et al., 2011). Only recent studies adopting the MDS criteria have begun to report language impairment (Cholerton et al., 2014; Goldman et al., 2013), with earlier studies describing PD-MCI as a decline in memory and frontal (attention/executive) functions (Aarsland et al., 2010). Whether variability in the prevalence of language deficits in PD-MCI is an artefact of the new MDS criteria, or reflects a cognitive domain not extensively assessed in preceding studies, is a direction for future research. Nonetheless, there is mounting evidence to indicate that people with PD-MCI demonstrate language impairment and the current study suggests that combining standard cognitive training with tDCS may alleviate this deficit.

The Standard Cognitive Training + tDCS group also improved on activities of daily living (g = .55) from pre-intervention to post-intervention, but improvements were not maintained at follow up. One study has reported improved

activities of daily living following standard cognitive training in PD (Pompeu et al., 2012). However, no tDCS studies have observed improvements in activities of daily living. Kim and Kim (2014) suggest that for older adults, compensation-focussed interventions will often induce frontally-mediated executive skills that transfer to practical improvements in daily activities. Specifically, Willis et al. (2006) found that compensation-focussed cognitive training of reasoning abilities in healthy older adults was associated with significantly less decline in activities of daily living for up to five years post-intervention. For the current study, anodal tDCS provided compensatory activation of the left DLPFC. This, paired with standard cognitive training, may have evoked improved frontally mediated executive skills (i.e., executive function improved in this group) that transferred into practical improvements in activities of daily living (e.g., eating tasks, dressing, doing hobbies).

The final intervention group in this study completed tailored cognitive training and tDCS. This group were therefore exposed to the *stimulation* and *compensation-focussed* aspects of tailored cognitive training, paired with the additional *compensation-focussed* aspects of tDCS (Kim & Kim, 2014). The Tailored Cognitive Training + tDCS group demonstrated significant improvement on executive function (SOC) from pre-intervention to post-intervention (g = .41), and these improvements were maintained at follow up (g = .23). Among studies that have examined these interventions independently, executive function improvements have been observed following tailored cognitive training and tDCS in PD (Disbrow et al., 2012; Pereira et al., 2013; Sammer et al., 2006). Reuter et al. (2012) compared the multimodal efficacy of cognitive training (Group A), cognitive training + transfer training (Group B), and cognitive training + transfer training + motor training (Group C) for people with PD-MCI. Post-intervention, Group C demonstrated the greatest significant improvement on executive function tasks (Reuter et al., 2012). At a 6-month follow up, only Group C had maintained improvements in executive function. Reuter et al.'s (2012) study did not include tDCS, but these findings suggest that combining tailored (compensation-focussed) cognitive training, with tailored (compensation-focussed) transfer training, and standard (stimulation-focussed) motor training may improve executive function in people with PD-MCI.

The Tailored Cognitive Training + tDCS group also improved on attention/working memory (LNS) from pre-intervention to follow up (g = .22), but no immediate post-intervention improvements were observed. As previously noted when describing results for the Tailored Cognitive Training group, one tailored cognitive training study reported significant improvement in attention in PD (Cerasa et al., 2014). Their study implemented group-based cognitive training, which may have accounted for the difference between their immediate beneficial effects and the current study's delayed effects on attention/working memory. For the Tailored Cognitive Training + tDCS group, however, there is evidence from healthy older adults to support the delayed effects of tDCS on cognition. Hsu, Zanto, Anguera, Lin, and Gazzaley (2015) reported that compared to participants who experienced sham followed by real-tDCS (1-hour apart) over the left DLPFC, those who received real followed by sham-tDCS demonstrated increased multitasking abilities. This finding suggests a delay in cognitive improvement following real-tDCS. Conversely, one study in PD has reported significant improvement on attention/working memory immediately following tDCS (Boggio et al., 2006). Several reasons have been suggested to account for the variability in results. Namely, tDCS is relatively nonfocal and when targeting a cortical region associated with many complex cognitive functions (e.g., DLPFC) in people with a neurodegenerative disorder (e.g., PD-MCI), their impaired cognitive networks may alter the responsiveness of the brain to tDCS (Olma et al., 2013) and the extent to which beneficial effects are observed (Barbey, Koenigs, & Grafman, 2010). For people with PD-MCI, anodal tDCS may temporarily affect cognitive networks associated with specific domains of impairment, resulting in improved cognition (Biundo et al., 2015). Conversely, individuals with PD but without MCI may experience minimal or limited beneficial effects of tDCS to their unimpaired cognitive networks, and consequently demonstrate no improvements in cognition. It is apparent, however, that tDCS may induce immediate or delayed beneficial effects on attention/working memory, which are associated with an individual's degree of neurodegeneration and presentation of cognitive impairment.

Memory (Paragraph recall) improved from pre-intervention to post-intervention (g = 1.36) for the Tailored Cognitive Training + tDCS group, and improvements were maintained at follow up assessment (g = 1.75). This is the first

study to report significant improvement in memory following tailored cognitive training and tDCS. Standard cognitive training paired with tDCS has recently shown memory improvements in PD-MCI, suggesting that combining these nonpharmacological interventions may alleviate memory deficits for people with PD (Biundo et al., 2015). To date, no studies administering tDCS independently have reported improvements in memory in PD or PD-MCI. Although from three published studies, only one (Pereira et al., 2013) included a standardised neuropsychological measurement of memory performance. Currently, one tailored cognitive training study has reported memory improvements in people with PD and PD-MCI (Naismith et al., 2013). All other published trials (excluding Reuter et al., 2012) have implemented interventions designed to train specific cognitive domains other than memory (e.g., executive function training to improve executive function; Sammer et al., 2006). Including a neuropsychological outcome (e.g., for memory) that is not representative of an intervention's proposed mechanism of action (e.g., cognitive training involving visuospatial skills), will be less likely to improve post-intervention. Memory impairment is common in PD-MCI (see Chapter 2.3.4) and may predict progression to PD-Dementia (Muslimovic et al., 2007). Future clinical trials of tDCS and tailored cognitive training need to include standardised memory outcomes and design interventions to target memory impairment in PD-MCI.

Lastly, the Tailored Cognitive Training + tDCS group demonstrated significant improvement on language (Similarities, g = 1.06) from pre-intervention to post-intervention, but improvements were not maintained at follow up. As with the Standard Cognitive Training + tDCS group, this is first study to report significant improvement in language following a combined tailored cognitive training and tDCS intervention for PD-MCI. For the Tailored Cognitive Training + tDCS group, there may be a specific reason as to why language improved in this group. Language improvements were observed on the Similarities test, but not the BNT. The MDS Task Force classify the Similarities test as a measure of language abilities (Litvan et al., 2012). However, the Similarities test is a subtest of the verbal IQ index of the WAIS battery of cognitive performance and involves abstract reasoning (Wechsler, 2008). Abstract reasoning is a higher-order cognitive ability associated with executive function and involves ordering, comparing, analysing, and synthesizing information to arrive at an answer (Lezak et al., 2012). When completing the

Similarities test, participants need to describe in what way are two concepts/words alike (e.g., "...in what way are 'acceptance' and 'denial' alike?"), and this task requires the use of abstract reasoning (an executive skill) to synthesise information related to both concepts/words. As a task requiring executive function, completing the Similarities test may involve increased activation of the left DLPFC, which was also the target of tDCS for this group of participants. Compared to participants who completed the other interventions, participants in this group demonstrated the lowest baseline score for the SOC test (i.e., greatest potential to benefit from the intervention), and demonstrated significant post-intervention improvement on this executive function outcome. Participants in this group demonstrated impaired executive function and completed cognitive training tasks tailored to executive function skills. Pairing this form of tailored cognitive training with tDCS applied to the left DLPFC may have increased cortical activity associated with improved performance on SOC *and* Similarities, tasks involving executive *and* language abilities.

To summarise, the Standard Cognitive Training group improved on three outcomes (memory, activities of daily living, and quality of life), the Tailored Cognitive Training group improved on two outcomes (attention/working memory and quality of life), the tDCS group improved on two outcomes (attention/working memory and memory), the Standard Cognitive Training + tDCS group improved on four outcomes (executive function, attention/working memory, language, and activities of daily living), the Tailored Cognitive Training + tDCS group improved on four outcomes (executive function, attention/working memory, memory, and language), and the control group did not improve on any outcome measures. A greater number of outcomes improved for the groups that received standard cognitive training combined with tDCS and tailored cognitive training combined with tDCS. Combining these interventions targeted impaired cognitive domains with potential for improvement, while stimulating neuronal plasticity in otherwise unimpaired domains (Kim & Kim, 2014). These results suggest that the theoretically additive benefits of stimulation and compensation-focussed interventions may lead to greater improvements in cognition and practical outcomes for people with PD-MCI. In other words, combining cognitive training with tDCS may provide optimal conditions for neuronal plasticity, leading to improvements in cognitive function.

4.6.2 Limitations

Several outcomes did not improve across intervention groups, which may be due to a number of reasons. Despite selecting outcomes in accordance with MDS Task Force recommendations (Litvan et al., 2012), a lack of sensitivity of some cognitive tests for detecting change in PD may have contributed to nonsignificant improvement for those tests. No improvements were observed on the Hopkin's Verbal Learning Test (HVLT). The HVLT has been predominantly validated for detection of severe cognitive decline in dementia populations (Strauss et al., 2006). For example, the total score from the HVLT has shown to be more sensitive than the MMSE in detecting dementia (Hogervorst et al., 2001), and using a diagnostic cut off of 1 SD below normative data has demonstrated to be 95% sensitive and 83% specific in detecting dementia (Shapiro, Benedict, Schretlen, & Brandt, 1999). In addition, several recent cognitive training studies in PD and PD-MCI reported no improvements on similar verbal memory tests (París et al., 2011; Pena et al., 2014; Zimmermann et al., 2014). Therefore, the HVLT may not be sensitive to mild changes in cognition following an intervention in PD.

No improvements were observed on the Boston Naming Test (BNT) or the Controlled Oral Word Association Test (COWAT). The COWAT is highly sensitive to frontally mediated deficits associated with PD, while the BNT is less sensitive and a more reliable indicator of moderate to severe dementia (Lezak et al., 2012). For the purpose of the current study, the BNT and COWAT were classified as language and executive function tests, respectively (Litvan et al., 2012). However, meta-analytic results identified a common use of semantic memory to complete both tasks, and individuals often demonstrate an equal and associated magnitude of impairment, on both tests in PD (Henry & Crawford, 2004). It is therefore possible that the BNT is not sensitive to mild language deficits or improvements in PD-MCI, but also that participants in the current study did not demonstrate a significant degree of semantic memory impairment or improvement (on the BNT or COWAT), following the cognitive training, tDCS, or cognitive training + tDCS interventions. The results from the current and previous studies suggest that the BNT may not be suitable for measuring subtle changes in language abilities in PD, suggesting that the MDS Task Force may need to reevaluate their recommendations for suitable language tests in PD-MCI (Litvan et al., 2012).

Recognised as the most widely used measure of global cognition, the Mini Mental State Examination (MMSE) was included as a primary outcome in this study. No intervention groups improved on the MMSE. The MMSE was first developed to assess frank dementia (Folstein et al., 1975) and has shown to be insensitive when detecting mild cognitive impairment in PD (Mamikonyan et al., 2009). Recommendations suggest that when using the MMSE to assess cognitive function in PD, it must be administered in conjunction with other cognitive tests, due to the MMSE's suboptimal specificity (54%) at the recommended screening cutoff point (Hoops et al., 2009). Results of this study suggest that the MMSE may have not been sensitive to improvements in global cognition following the cognitive training and tDCS interventions. The Parkinson's Disease-Cognitive Rating Scale (PD-CRS) was also included as a measure of global cognition, but following a Bonferroni correction due to multiple comparisons, post-intervention improvements were not statistically significant. Compared to the Control group, however, several intervention groups demonstrated improvements of medium effect on the PD-CRS, post-intervention (e.g., tDCS group, g = .53; Standard Cognitive Training + tDCS group, g = .71; see Appendix H). In addition, the PD-CRS has been designed to reliably discriminate between healthy controls, cognitive intact PD, PD-MCI and PDD groups (Pagonabarraga et al., 2008) and is recommended by the MDS Task Force to assess global cognition in PD. Interpretation of improvements on this outcome were therefore limited by statistical constraints (a Bonferroni correction), and not necessarily due to limitations of the PD-CRS or a lack of beneficial effects of cognitive training or tDCS on this outcome.

A limitation of this study was the lack of alternate forms for neuropsychological tests. Although common practice in many studies examining cognitive training and tDCS in PD (e.g., Doruk et al., 2014; Paris et al., 2011; Pena et al., 2014), the same neuropsychological tests were used at pre-intervention, post-intervention, and follow up. Using the same tests across assessment intervals may induce practice effects during the course of a clinical trial (Benedict & Zgaljardic, 1998). Participants may therefore demonstrate improvement on a neuropsychological test due to previous exposure to that test rather than improvement in the cognitive function being assessed (Troster, Woods, & Morgan, 2007). Although most participants in the current study provided anecdotal evidence indicating that they did

not remember completing the same neuropsychological tests at pre-intervention, this methodological limitation needs to be considered when interpreting the results.

The cognitive training and tDCS parameters used in this study may have impacted nonsignificant results. No improvements were observed for visuospatial abilities, as measured by Hooper's Visual Orientation Test (HVOT) and Judgement of Line Orientation (JLO). Successful completion of HVOT requires the use of perceptual organisation to rearrange pieces of an object (Strauss et al., 2006) and JLO primarily involves visual estimation of angled lines (Benton et al., 1994). The visuospatial activities administered as part of the computer-based cognitive training intervention in this study required identification of coordinates on a numbered grid and remembering time ranges on analog clocks following a perceptual delay (Smartbrain Pro^{TM}). It is possible that the visuospatial cognitive training tasks did not directly align with the visuospatial skills needed to complete HVOT and JLO. In addition, several hemispheric and lesion studies report more dominant involvement of the right posterior hemisphere (compared to the left) during completion of HVOT (Nadler, Grace, White, Butters, & Malloy, 1996) and JLO (Gur et al., 2000; Ng et al., 2001; Ng et al., 2000). In this study, tDCS was applied to a cortical region that is not associated with visuospatial performance (the left DLPFC). Stimulation of the left DLPFC was therefore not likely to improve visuospatial abilities. The current results support recent cognitive training studies (Cerasa et al., 2014; Petrelli et al., 2014; Zimmermann et al., 2014) and a tDCS study (Doruk et al., 2014), which also reported no improvement in visuospatial tasks. It is recommended that future trials match visuospatial cognitive training activities with the visuospatial abilities assessed by standardised cognitive tests, and explore the potential of noninvasive brain stimulation over the right posterior hemisphere for improving visuospatial function in people with PD-MCI.

The current study was limited by the lack of neuroimaging (e.g., fMRI) to examine whether the different interventions were associated with homogeneous or heterogeneous patterns or changes in cortical activation. One tDCS study in PD has administered fMRI immediately following stimulation and reported functional network changes in left DLPFC and left temporo-parietal cortex, which were associated with verbal fluency performance (Pereira et al., 2013). fMRI has also been

administered following cognitive training in PD. Cerasa et al. (2014) reported activation of the superior parietal cortex associated with increased attentional performance and activation of the DLPFC associated with increased executive function. It could be inferred that similar networks of activation may have been present in the cognitive training, tDCS, and cognitive training + tDCS groups in the current study. However, definitive conclusions cannot be made about whether stimulation focussed or compensation focussed interventions induce the greatest degree of synaptic plasticity and associated improvement in cognitive function for people with PD-MCI.

Identifying PD-MCI using a cutoff of one standard deviation (SD) below normative data may have been a limitation in the current study. Although within recommendations of the MDS Task Force, PD-MCI is highly heterogeneous and a proportion of individuals often return back to normal cognition, due to normal fluctuations and effects of medication on cognitive functioning (Loftus et al., 2015; Yarnall, Rochester, & Burn, 2013). Using the most liberal (<1 SD) cutoff may have resulted in false-positive diagnoses of PD-MCI (i.e., including participants with normal cognition), when participants were experiencing a mild and temporary fluctuation in their cognitive functioning. Capturing false-positive diagnoses at pre-intervention assessments may then result in people 'reverting' back to normal cognition at post-intervention and follow-up assessments, which compromises the reliability of the interventional effects. Having said this, daily levodopa equivalent dose was controlled in statistical analyses and all neuropsychological assessments were completed during participants' 'ON' stage of medication use. Controlling these factors would limit the likelihood of false-positive diagnoses.

Final limitations of this study were the sample size and the lack of matching exposure between intervention groups. For sufficient statistical power, 54 participants (9 per group) were needed to detect moderate effects (Faul et al., 2007). However, only 42 participants met inclusion criteria and 4 participants dropped out prior to follow up assessment. Although larger than the average sample size (N = 34, see Chapter 3) of previous controlled trials of cognitive training and non-invasive brain stimulation in PD, this study was somewhat underpowered which may have impacted the nonsignificant results. Participants allocated to the cognitive training

groups (standard or tailored) completed 12 sessions of training. Whereas, participants in the cognitive training + tDCS groups completed 12 sessions of cognitive training *and* 4 sessions of tDCS. Completing both interventions exposed participants to a greater number of therapeutic sessions designed to improve cognition. Additional therapeutic sessions may have therefore produced purely additive beneficial effects on neuropsychological outcomes due to increased exposure during the intervention. Lastly, six outcomes demonstrated no significant improvement following the intervention and several hypotheses were either not, or only partially, supported. As noted in Chapter 3, research examining nonpharmacological interventions for PD-MCI is in its relative infancy and the results of this study need to be interpreted as preliminary findings.

4.6.3 Directions for Future Research

Future studies examining the therapeutic potential of cognitive training and tDCS need to include neuropsychological outcomes that are sensitive to changes in cognition in PD-MCI. Goldman et al. (2015) reported the first recommendations for the most optimal number (10 tests, 2 per domain) and selection of tests for measuring cognitive performance in PD. However, the Trail Making Test (Part A) was recommended as a better performing measure of attention/working memory deficits, which conflicts with previous studies reporting low sensitivity of the Trail Making Test (Part A) for detecting frontal impairments in PD (Kaszás et al., 2012). More studies are needed to determine which neuropsychological tests are most appropriate for identifying impairments and measuring change in PD-MCI, and future researchers need to ensure that alternate forms of neuropsychological tests are used to limit potential practice effects in clinical trials (for exhaustive compendiums of tests see: Lezak, Howieson, & Loring, 2012 and Strauss et al., 2006).

Methodological parameters of cognitive training and tDCS interventions need to be considered in future clinical trials. The results of this study suggest that the visuospatial outcomes may have not been representative of the visuospatial skills needed to complete the computer-based visuospatial activities. In addition, applying tDCS to the left DLPFC was not likely to improve visuospatial abilities that are predominantly mediated by the right posterior hemisphere. Future studies need to

implement cognitive training modalities (e.g., standard and/or tailored) and tDCS locations (e.g., DLPFC, posterior cortices) which consider the outcomes most representative of each intervention's cognitive functions targeted for improvement.

Neuroimaging (molecular, structural, and functional) has significantly expanded our understanding of the complex neurobiological changes associated with PD (Weingarten, Sundman, Hickey, & Chen, 2015). For example, imaging techniques discovered the cortico-basal ganglia-thalamocortical dorsolateral prefrontal cortex loop, which is implicated by dopamine depletion from the putamen to the dorsal caudate, and associated with executive function decline in PD (Weingarten et al., 2015; Xu et al., 2016). Studies utilising imagine techniques have also demonstrated the important impact of hippocampal degeneration which often leads to memory impairment in the later stages of PD (Calabresi, Castrioto, Di Filippo, & Picconi, 2013). Including neuroimaging as a primary outcome in future cognitive training and tDCS studies will provide evidence of any cognitive changes indicated by neuropsychological tests, and explore whether individuals with single or multiple domain cognitive impairments demonstrate greater cortical activation post-intervention and are more likely to benefit from these therapeutic effects.

Future studies may want to implement a more conservative cut off score (e.g., < 2 SDs below normative data) for identification of PD-MCI. A more conservative diagnostic criterion would reduce the possibility of including participants who demonstrate a temporary and mild decline in cognition, and whom do not meet a formal identification of PD-MCI (Yarnall et al., 2013). The use of 2 SDs below normative data as an indicator of impaired performance on a neuropsychological test has demonstrated good sensitivity and specificity in PD-MCI (Goldman et al., 2013). It is important to note, however, that severe cognitive decline can negatively impact cognitive abilities beyond the potential of cognitive training or tDCS, resulting in participants that may not respond to nonpharmacological interventions (Kim & Kim, 2014). It is therefore suggested that future studies examine the potential of these interventions within populations of varying age, cognitive impairment, years of education, disease duration, and severity of Parkinsonian symptoms. Conducting rigorous RCTs of cognitive training and tDCS across the spectrum of the disease course (e.g., de novo to advanced PD) has the potential to determine if and when

these interventions (stimulation and compensation focussed) are most efficacious for preventing, alleviating, and potentially halting, the progression of cognitive decline in PD-MCI.

Results from this study suggest that tailored cognitive training, tDCS, tailored cognitive training + tDCS, and standard cognitive training + tDCS can lead to long-term improvements (12 weeks) in executive function, attention/working memory, memory, and quality of life. As explained, very few previous trials of these interventions have included long-term follow-up assessments of cognition and practical outcomes. It is therefore recommended that future studies include follow-up assessments (e.g., 3, 6 and 12 months) to build upon the current results, and to explore whether the individual or combined therapeutic potential of these interventions are more likely to lead to long-term improvements cognition, activities of daily living, and quality of life for people with PD-MCI.

4.7 Chapter Summary

This chapter presented the findings of the first randomised controlled trial of standard cognitive training, tailored cognitive training, tDCS, standard cognitive training + tDCS, and tailored cognitive training + tDCS for mild cognitive impairment in PD. This study had several strengths. First, this clinical trial was conducted in accordance with the CONSORT statement for RCTs of nonpharmacological interventions (Boutron et al., 2008) and provides Level III evidence in support of cognitive training, tDCS, and cognitive training + tDCS for PD-MCI. Second, the rate of participant attrition was low (< 10%) with only 4 participants dropping out of the study prior to follow-up assessments. Third, cognitive performance was measured using an extensive battery of neuropsychological tests, in-line with MDS Task Force recommendations for Level II diagnostic criteria of PD-MCI. Results of this study supported previous clinical trials suggesting that cognitive training and tDCS can improve executive function, attention/working memory, and memory in PD. However, this study was the first to explore the combined therapeutic potential of cognitive training and tDCS. Results indicated that combining these therapeutic techniques may increase their potential to

alleviate deficits in cognition, activities of daily living, and quality of life for people with PD-MCI, as opposed to administering these interventions independently. It is recommended that future studies examine the effects of standard and tailored cognitive training and different parameters of tDCS (e.g., cortical site of stimulation), in combination with neuroimaging techniques, and among individuals at variable stages of PD, to determine the long-term efficacy of these nonpharmacological interventions for people with PD-MCI.

CHAPTER 5 General Discussion

5.1 Introduction

The overarching aim of this research was to examine the therapeutic potential of nonpharmacological interventions for mild cognitive impairment in Parkinson's Disease (PD-MCI). Three studies were conducted and the corresponding chapters provide a thorough discussion of each study's rationale, methodology, results, implications, limitations, and recommendations for future research. This final chapter will provide a summary of the research findings, followed by a discussion of the findings within the context of the current literature. This chapter will also provide recommendations for future studies examining cognitive training and brain stimulation interventions for people with PD-MCI.

5.2 Summary of Research Findings

5.2.1 Study 1: Prevalence and Subtypes of Mild Cognitive Impairment in PD

Study 1 was the first application of the Movement Disorder Society (MDS) Task Force criteria for PD-MCI in an Australian sample of people with PD. There were several main findings from Study 1. First, 64.3% of participants met MDS Task Force criteria for PD-MCI when applying a 1 SD cut off to classify cognitive impairment on a neuropsychological test. Among those with PD-MCI, 93.4% presented with multiple domain impairment (i.e., impaired test performance in more than one cognitive domain). When examining individual cognitive domains, attention/working memory (66.7%), executive function (62.2%), and memory (66.7%) were most frequently impaired. The overall frequency of PD-MCI decreased from 64.3% to 28.6% after applying a 2 SD cut off to classify cognitive impairment. The frequency of subtype classifications remained stable, with multiple domain impairment maintained as the most frequent subtype (90%) even when using this more stringent cut off.

The second main finding from Study 1 was that compared to participants with normal cognition, participants classified as PD-MCI performed significantly worse across all cognitive domains (excluding one test of executive function, Stockings of Cambridge, p = .76). However, participant groups (PD-MCI vs Normal Cognition) did not differ on demographic variables (e.g., age, years of education, disease duration). The findings from Study 1 provide evidence to support the heterogeneous presentation of cognitive impairments in PD-MCI. Compared to individuals with normal cognition and PD, those with PD-MCI may perform significantly worse across the spectrum of cognitive domains.

5.2.2 Study 2: A Meta-Analysis of Cognitive Training and Non-Invasive Brain Stimulation for Cognition in PD

Study 2 was the first meta-analysis of randomised controlled trials of standard and tailored cognitive training and non-invasive brain stimulation for the improvement of cognition in PD. The only controlled trial of tDCS did not provide sufficient data for inclusion and was therefore excluded from the study. There were several main findings in Study 2. First, improvements in executive function were observed when standard and tailored cognitive training studies were combined (g = .42; 95% CI = .15 to .68). When standard and tailored cognitive training were considered separately, the tailored effect estimate reduced to non-significance (g = .30; 95% CI = -.16 to .76). Two rTMS studies were included in the meta-analysis (Benninger et al., 2011; Benninger et al., 2012), but did not statistically improve executive function (g = .40, 95% CI = -.14 to .93). Second, significant pooled effects for attention/working memory were observed when standard and tailored cognitive training were combined (g = .23, 95% CI = .02 to .44) and for standard cognitive training alone (g = .29, 95% CI = .04 to .53). Similar to the results for executive function, only one rTMS study examined attention/working memory and the effect was not significant (g = .34, 95% CI = -.42 to 1.11). The third and final significant finding from Study 2 was that both standard and combined cognitive training studies improved memory in PD (standard: g = .35, 95% CI = .03 to .66; combined: g = .33, 95% CI = .06 to .59). No significant pooled effects were identified for visuospatial abilities, language, and global cognition.

Study 2 provided a synthesis of results from all published controlled trials of standard cognitive training, tailored cognitive training, tDCS, and rTMS studies in PD. The findings from Study 2 indicated that standard and tailored cognitive training may improve executive function, attention/working memory, and memory.

5.2.3 Study 3: A Randomised Controlled Trial of Cognitive Training and Transcranial Direct Current Stimulation in PD-MCI

Study 3 was the first randomised controlled trial comparing standard cognitive training, tailored cognitive training, tDCS, standard cognitive training + tDCS, and tailored cognitive training + tDCS for mild cognitive impairment in PD. Overall, differential rates of statistically significant improvements in cognition, activities of daily living, and quality of life were observed across the intervention groups.

The Standard Cognitive Training group improved on memory (F [2, 104] = 5.24, p = .007), activities of daily living (F [2, 104] = 11.29, p < .001), and quality of life (F [2, 95] = 7.21, p = .001), and the Tailored Cognitive Training group improved on attention/working memory (F [2, 95] = 6.62, p = .002) and quality of life (F [2, 95] = 12.48, p < .001). Study 3 was the first randomised controlled trial to report improved quality of life following standard or tailored cognitive training in people with PD-MCI.

The tDCS group improved on attention/working memory (F [2, 103] = 4.06, p = .020) and memory (F [2, 104] = 17.82, p < .001), and the Standard Cognitive Training + tDCS group improved on executive function (F [2, 93] = 10.70, p < .001), attention/working memory (F [2, 103] = 35.05, p < .001), language (F [2, 92] = 5.23, p = .007), and activities of daily living (F [2, 104] = 3.40, p = .037). The final intervention group completed tailored cognitive training + tDCS and improved on executive function (F [2, 93] = 12.00, p < .001), attention/working memory (F [2, 95] = 5.11, p = .008), memory (F [2, 104] = 12.09, p < .001), and language (F [2, 92] = 17.43, p < .001). Study 3 was the first RCT of cognitive training and/or tDCS to report improvements in language abilities in PD and PD-MCI.

The findings from Study 3 suggest that cognitive training, tDCS, and cognitive training combined with tDCS may improve executive function, attention/working memory, memory, language, activities of daily living, and quality of life for people with PD-MCI.

5.3 Mild Cognitive Impairment in PD: Contribution of Research Findings to the Current Literature

In addition to the cardinal motor symptoms of PD, it is now acknowledged that a significant proportion of people with PD experience impaired cognitive functioning (Goldman & Weintraub, 2015). Cognitive deficits are associated with a multitude of symptoms that worsen quality of life in PD (Zhang et al., 2016), and the increasing prevalence of PD-MCI, highlights the need for research to explore the potential of pharmacological and nonpharmacological interventions for alleviating and potentially halting the progression of cognitive impairments in PD.

5.3.1 Heterogeneity of PD-MCI

Research indicates that cognitive impairment is highly heterogeneous in PD (Goldman & Weintraub, 2015; Kehagia et al., 2010). Individuals often present with differing combinations of impairments across the spectrum of cognitive domains (Cholerton et al., 2014; Marras et al., 2013). The findings from Study 1 support and extend the understanding of PD-MCI. Study 1 demonstrated that at a 1 SD cut off or 2 SD cut off below normative data, 64% (at a 1 SD cut off) and 28% (at a 2 SD cut off) of participants met the diagnostic criteria for PD-MCI. At both cut off levels, multiple domain impairment was more prevalent (93% to 90%) than single domain impairment (7% to 10%). Furthermore, 20 different patterns of impairments were identified at 1 SD and 10 different patterns of impairments identified at 2 SDs. Irrespective of the severity of cognitive impairments in Study 2, PD-MCI was heterogeneous and included deficits across all cognitive domains.

Studies examining neuropsychological and cognitive deficits in PD-MCI describe and subtype behavioural representations of cognitive impairments (Kalbe et

al., 2016), but these studies do not explore the underlying pathophysiological processes that lead to the development of cognitive impairments in PD. Research is beginning to address the role of genetic characteristics and protein/neurotransmitter abnormalities, and their association with PD-MCI (Cosgrove et al., 2015). For example, Williams-Grey (2009) and colleagues examined longitudinal (5 year) changes of catecholaminergic and cholinergic deficits in PD. For those with PD-MCI, executive function impairment was associated with catecholaminergic changes involving frontostriatal dopaminergic deficits, but limited cholinergic interaction. For those with PD-Dementia, early cholinergic deficits were the prominent factor associated with severe cognitive decline (Williams-Gray et al., 2009). A review of biomarkers and treatments of cognitive impairment in PD (Svenningsson et al., 2012), reported acetylcholine deficiency in posterior cortical regions as a biomarker contributing to memory, language and visuospatial deficits. In addition, Kehagia et al. (2010) proposed the 'dual syndrome' hypothesis to describe how two distinct genetic syndromes (executive and posterior cortical) may be associated with executive function and memory/visuospatial abilities in PD. Nombela et al. (2014) recently supported this hypothesis by demonstrating that a specific genetic variation (rs4680 polymorphism of the COMT gene) modulated executive function and two other genetic variations (APOE allelic and MAPT haplotype) independently modulated posterior cortical functions of memory and visuospatial abilities, respectively. These studies provide preliminary evidence to suggest that neurotransmitter abnormalities and genetic characteristics are associated with cognitive impairments in PD, and that these factors may predispose the onset of cognitive decline in PD and other neurodegenerative disorders.

The findings from Study 1 support the results from recent neuropsychological and pathophysiological studies indicating that PD-MCI is highly heterogeneous. PD-MCI involves complex pathological changes across multiple cortical regions, and those changes may present as mild, moderate, and severe deficits in cognitive function for people with PD.

5.3.2 Diagnostic criteria for PD-MCI

Due to the heterogeneous presentation of cognitive deficits in PD, a Movement Disorder Society (MDS) Task Force developed diagnostic criteria in attempt to standardise assessment of cognitive impairments (Litvan et al., 2012). Since the development of the PD-MCI criteria, several studies have examined its potential to accurately diagnose and subtype PD-MCI (Bezdicek et al., 2016; Goldman et al., 2013). Any standardised criteria developed for international use needs to be validated and examined across multiple populations, and Study 1 of this thesis was the first application of the MDS criteria for PD-MCI in an Australian sample.

Study 1 applied the Level II (comprehensive assessment) MDS criteria and identified the previously described presentation of cognitive impairments in PD-MCI. In summary, more than 60% of the sample met PD-MCI diagnostic criteria and the multiple domain subtype was significantly more prevalent than the single domain subtype. Studies preceding the MDS criteria often reported a much lower overall prevalence of PD-MCI (19% to 38%), and single domain impairment was reported as more frequent than multiple domain impairment (Caviness et al., 2007; Goldman et al., 2012; Litvan et al., 2011).

Study 1 identified several issues with the MDS criteria that may account for this variability between prevalence estimates and subtyping frequencies of PD-MCI. First, the new diagnostic criteria is less stringent when diagnosing multiple domain compared to single domain subtypes, which will invariably identify more people with multiple domain impairment (Goldman et al., 2013). The results of Study 1 accentuated this issue, with almost all participants with PD-MCI meeting the criteria for the multiple domain subtype. Second, variable use of SD cut off scores will produce varying estimates of the prevalence of PD-MCI. The findings from Study 1 accentuate this issue, with a significant proportion of participants (64%) meeting PD-MCI diagnosis at the 1 SD cut off and this figure reduced (28%) when using the 2 SD cut off. Third, differential weighting and selection of tests per cognitive domain will likely bias subtyping statistics of PD-MCI. Study 1 did, however, control for this issue by administering an even number of tests (two) per cognitive domain. Several recent studies, however, administered an unequal number of tests (3 to 7) in an

attempt to validate the diagnostic criteria (Cholerton et al., 2014; Goldman et al., 2013). Using an unequal number of tests will increase the risk of Type 1 errors and may falsely inflate the frequency of PD-MCI (Loftus et al., 2015).

Despite the issues raised regarding the use of the MDS diagnostic criteria to identify PD-MCI, findings from Study 1 supported recent applications of the criteria (e.g., Geurtsen et al., 2014) and provided evidence to support its future refinement and utility (Bezdicek et al., 2016). Section 5.4.1 provides recommendations to address the issues with the current diagnostic criteria for PD-MCI.

5.3.3 Nonpharmacological interventions for PD and PD-MCI

Current research exploring pharmacological treatments (e.g., cholinesterase inhibitors and memantine) for PD-MCI provides preliminary evidence in support of their potential to alleviate cognitive impairments in PD (Goldman & Weintraub, 2015; Wang et al., 2014). Many people with PD are, however, burdened by polypharmacy and experience a range of adverse side effects due to pharmacological treatments (Lai et al., 2011). Recent clinical trials have examined the potential of nonpharmacological interventions (e.g., cognitive training and non-invasive brain stimulation) for cognitive impairments in PD, and provide evidence to support their beneficial effects on cognition (Boggio et al., 2005; París et al., 2011). Study 2 reviewed all controlled and uncontrolled trials of standard cognitive training, tailored cognitive training, tDCS, and rTMS. Significant methodological differences were identified across studies, which limited interpretation of the beneficial effects of these interventions. Study 2 therefore included a meta-analysis of all controlled trials to provide an accurate estimate of the potential of these interventions for improving cognition in PD.

Study 2 identified that standard and tailored cognitive training may improve executive function, attention/working memory, and memory in PD. No beneficial effects were identified for rTMS on cognition in PD, and the only controlled trial of tDCS did not provide sufficient data to be included in the meta-analysis. Overall, the findings from Study 2 suggested that cognitive training may alleviate deficits in executive function, attention/working memory, and memory in PD, but the findings were limited by the few controlled trials available for meta-analysis. In accordance

with the conclusions from Study 2 and as recommended by Hindle et al. (2013), "...there is an urgent need for rigorous RCTs of nonpharmacological, noninvasive treatments for cognitive impairment and dementia in PD" (p. 1048).

To address this gap in the literature, Study 3 used an RCT design to compare standard cognitive training, tailored cognitive training, tDCS, standard cognitive training + tDCS, and tailored cognitive training + tDCS for improvement of cognition, activities of daily living, and quality of life in PD-MCI. In accordance with Kim and Kim's (2014) theoretical framework, standard cognitive training is a stimulation-focussed intervention that broadly enhances cognitive function by changing existing neural connections in the brain. Tailored cognitive training is a stimulation and compensation-focussed intervention aimed at improving specific cognitive functions that have been impacted by neural degeneration (Kim & Kim, 2014). The tDCS used in this study was a compensation-focussed intervention to increase cortical activity in the left DLPFC. The Scaffolding Theory of Ageing and Cognition suggests that older adults experience increased compensatory activation (i.e., 'scaffolding') of secondary neural circuits in the prefrontal cortices, when primary neural circuits are diminished during a complex cognitive task (Goh & Park, 2009). tDCS therefore provided additional compensatory activation of the left DLPFC for people with PD-MCI. In Study 3, standard cognitive training combined with tDCS and tailored cognitive training combined with tDCS were stimulation and compensation focussed interventions, designed to provide optimal conditions for neural plasticity and associated improvements in cognition.

5.3.3.1 Standard Cognitive Training. In Study 3, the Standard Cognitive Training group improved on memory, activities of daily living, and quality of life. Previous studies had demonstrated significant improvements in memory and activities of daily living following standard cognitive training in PD (Petrelli et al., 2014; Pompeu et al., 2012). Study 3 was the first RCT to report improved quality of life. París et al. (2011) administered the same cognitive training software (Smartbrain Pro^{TM}), but found no change in quality of life outcomes. This null result may have been impacted by a ceiling effect during cognitive training, given that Paris et al.'s (2011) sample included participants without cognitive impairments (i.e., participants without the ability to improve their cognition). Nonetheless, cognitive impairment is

associated with worsened quality of life for people with PD (Klepac et al., 2008), and Study 3 was the first clinical trial to provide evidence in support of standard cognitive training for improving this domain.

5.3.3.2 Tailored Cognitive Training. The Tailored Cognitive Training group improved on attention/working memory and quality of life. The beneficial effect of tailored cognitive training on attention/working memory was delayed with no immediate post-intervention improvement, but presented 12-weeks post-intervention cessation. One tailored cognitive training study has reported immediate improvements in attentional abilities post-intervention (Cerasa et al., 2014). This study, however, conducted group-based cognitive training which may have provided additional therapeutic effects (e.g., social interaction) leading to immediate (as opposed to delayed) improvements in attention/working memory. The Tailored Cognitive Training group also improved on quality of life and Study 3 was the first trial in PD to report improvements in this domain following tailored cognitive training. The neurobiological mechanism responsible for improvement in quality of life following cognitive training is currently not known. Research in dementia suggests that the beneficial effects of cognitive training for quality of life may be reliant upon cognitive improvement during training, and quality of life is less likely to improve if no cognitive benefits are observed (Woods et al., 2006). Study 3 provides preliminary evidence to suggest that tailored cognitive training, a stimulation and compensation-focussed intervention, may induce neural plasticity that acts to improve attention/working memory and quality of life in people with PD-MCI.

5.3.3.3 Transcranial Direct Current Stimulation (tDCS). In Study 3, the tDCS group improved on attention/working memory and memory. These results were supported by earlier studies examining the effects of tDCS in PD and AD. Boggio et al. (2006) demonstrated improvements in attention/working memory following tDCS in PD, and three studies in AD reported improved memory following tDCS (Boggio et al., 2012; Boggio et al., 2009; Ferrucci et al., 2008). For Study 3, the proposed mechanism of action for tDCS was considered in accordance with Scaffolding Theory of Ageing and Cognition (Goh & Park, 2009). These findings therefore suggest that anodal tDCS over left DLPFC may induce compensatory

activation of cortical networks associated with attention/working memory and memory in PD-MCI, and thereby alleviate impairment in these cognitive domains.

5.3.3.4 Standard Cognitive Training + tDCS. The Standard Cognitive Training + tDCS group improved on executive function, attention/working memory, language, and activities of daily living. A number of studies have combined cognitive training with non-invasive brain stimulation (tDCS and rTMS) in AD and one study has explored the combination of these interventions in PD. These studies reported improvements in attention and memory (Biundo et al., 2015) and global cognition (Bentwich et al., 2011; Rabey et al., 2013), but no beneficial effects for executive function, language, or activities of daily living. Study 3 was the first RCT of cognitive training and tDCS to report improvements in language abilities and activities of daily living in PD-MCI. The novelty of these findings may be the consequence of no cognitive training, rTMS or tDCS studies having included a standardised measurement of language abilities in PD (Litvan et al., 2011). In addition, only one previous cognitive training study has provided evidence to support a nonpharmacological intervention for improving activities of daily living (Pompeu et al., 2012). Despite the limited evidence available to support these results, Study 3 demonstrated that standard cognitive training combined with tDCS may have induced stimulation and compensation-focussed effects on neural activity to improve cognitive function and activities of daily living in PD-MCI.

5.3.3.5 Tailored Cognitive Training + tDCS. In Study 3, the final intervention group completed tailored cognitive training + tDCS and improved on executive function, attention/working memory, memory, and language domains. Several studies examining the potential of cognitive training and tDCS independently, have also reported improvements in executive function (Pereira et al., 2013), attention/working memory (Boggio et al., 2006; Cerasa et al., 2014), memory (Naismith et al., 2013). Study 3 was the first RCT of tailored cognitive training and tDCS to report improvements in language abilities in PD-MCI. As noted in Chapter 4.6.1, the improvement in language abilities in this group may be attributed to the increased activation of the left DLPFC following tDCS and the use of executive skills (i.e., abstract reasoning) to complete the language task (Similarities test), which are also mediated by cortical networks within the left DLPFC. Tailored cognitive

training + tDCS may therefore induce neural plasticity as a stimulation and compensation-focussed intervention, thereby alleviating cognitive deficits in PD-MCI.

Overall, Study 3 demonstrated that compared to the groups that received cognitive training or tDCS independently, a greater number of outcomes improved for the groups that received cognitive training *combined* with tDCS. This result suggests that combining stimulation and compensation-focussed interventions may lead to greater improvements in cognition and practical outcomes for people with PD-MCI. These findings add to the current literature to support nonpharmacological interventions as potential therapies for improving deficits in cognition, activities of daily living, and quality of life for people with PD-MCI.

5.4 Recommendations for Future Research

Comprehensive recommendations and directions for future research were discussed in the preceding chapters. These recommendations are summarised in the following section.

5.4.1 Assessment and subtyping of cognition in PD-MCI

The findings from the research in this thesis highlighted several issues associated with the assessment and subtyping of PD-MCI. Specifically, future studies need to:

1. **Examine and report PD-MCI frequency statistics at differing diagnostic cut off scores.** This research identified that applying different standard deviation cut off scores to classify PD-MCI significantly influences the frequency statistics used to describe the prevalence of PD-MCI. Future studies need to report PD-MCI frequency statistics at 1, 1.5, and 2 SD cut off scores to explore whether cognitive impairments and subtype classifications are associated with increasing severity of PD-MCI. Reporting these statistics will ensure future studies are transparent in their assessment of PD-MCI and will increase the broader understanding of these cognitive impairments in PD. This will also translate to the allied

health setting in terms of informing diagnosis of PD-MCI.

2. **Report sources of normative data that are used to establish diagnoses of PD-MCI.** Selecting appropriate normative data is equally as important as choosing a reliable and valid neuropsychological test (Strauss et al., 2006). Using normative data that is not a demographic match to a participant's characteristics may lead to false-positive or false-negative classifications of PD-MCI, impacting the accuracy of prevalence and subtyping statistics. Therefore, future studies need to provide a description and reference list of their normative data sets to ease exposition and interpretation of their results. Reporting sources of normative data sets in peer-reviewed journals will also provide physicians and geriatricians with comparative statistics for accurate diagnoses and potentially increase community and government awareness of mild cognitive impairment in PD.

3. **Explore the diagnostic accuracy of a more conservative criterion for the multiple domain subtype of PD-MCI.** The current MDS criteria for PD-MCI classifies individuals as the multiple domain subtype if they demonstrate impaired performance on one neuropsychological test in any two or more cognitive domains. The single domain subtype applies a more conservative criterion and requires impaired performance on two neuropsychological tests in any one domain. The more liberal criterion for the multiple domain subtype may be associated with the recent increase in the frequency of multiple domain PD-MCI. Among participants classified as PD-MCI, Study 1 identified more than 90% of those participants as the multiple domain subtype. Future studies need to explore what effect a conservative criterion (i.e., impairment on two tests in any two or more domains) will have on frequency estimates of multiple domain PD-MCI and whether this criterion will increase diagnostic accuracy of cognitive impairments in PD.
4. **Administer a consistent and equal number of neuropsychological tests to each cognitive domain.** Study 1 addressed this issue by including two neuropsychological tests per cognitive domain. However, recent

studies have applied an inconsistent number and weighting of tests to cognitive domains (e.g., Cholerton et al., 2014), which increases the risk of Type I errors and may inflate the frequency of PD-MCI. In accordance with recommendations by Goldman et al. (2015), future studies should administer two tests per cognitive domain to limit biases in the diagnosis and subtyping of PD-MCI.

5. **Apply consistent classifications of neuropsychological tests used to measure cognitive domains.** This research identified that recent studies often varied when classifying neuropsychological tests to specific cognitive domains. There is considerable overlap across many cognitive abilities (e.g., executive function and working memory) and neuropsychological tests often involve the use of more than one cognitive ability. For research purposes, however, consistent classification of neuropsychological tests will increase the generalisability of research findings and assist with standardised examination of cognitive impairments in PD-MCI. For health professionals, consistency across research will provide evidence to increase uniformity of cognitive assessments in clinical settings and assist with referrals to appropriate specialist and treatment services for people with PD-MCI.

6. **Include standardised assessment of processing speed.** The MDS criteria for PD-MCI does not identify processing speed as an independent cognitive domain (Litvan et al., 2012), yet impaired processing speed is often associated with worse performance on specific neuropsychological tests (e.g., for executive function) in PD. It is recommended that future studies include standardised assessment of processing speed to account for potential comorbid associations between cognitive domains and increase the current understanding of impaired processing speed in PD-MCI.

5.4.2 Methodological Parameters of Cognitive Training and tDCS Interventions

Studies 2 and 3 identified a number of methodological parameters as limiting factors. Future clinical trials need to:

1. **Recruit a large sample to ensure sufficient statistical power in RCTs.** Study 3 required 54 participants (9 per group) to ensure sufficient statistical power. Only 42 participants (7 per group) met inclusion criteria. Study 3 was somewhat underpowered and this factor may have affected the non-significant results. It is difficult to recruit large groups of participants for clinical trials in PD, specifically in the advanced stages of the disease when individuals lose their ability to function independently (i.e., a caregiver is required for travel and daily activities). It is recommended, however, that future RCTs exploring the potential of cognitive training and tDCS ensure they recruit participant samples to satisfy the requirements of sufficient statistical power.

2. **Ensure cognitive outcomes align with the proposed mechanisms of action of cognitive training interventions.** This research identified that computer-based cognitive training programs include many cognitive tasks that require the use of different abilities, across the spectrum of cognitive domains. It is important that future researchers align the proposed mechanism of action of a cognitive training intervention (e.g., working memory) with those outcomes that actually assess the corresponding cognitive domain. Implementing this method will likely increase the probability of significant improvements in cognitive outcomes following cognitive training interventions. Determining which cognitive outcomes are most responsive to change following cognitive training interventions, will provide evidence for clinicians to recommend potential cognitive training programs and regimes to alleviate cognitive deficits and improve quality of life for people with PD-MCI.

3. **Use neuropsychological outcomes that are sensitive to changes in cognition in PD-MCI.** This research highlighted that some neuropsychological outcomes used in previous studies and recommended

by the MDS Task Force, may not be sensitive to changes in cognition in PD-MCI. Including these outcomes in RCTs of cognitive training and tDCS will often result in null post-intervention effects and potentially underestimate the beneficial effects of these interventions on cognition. It is recommended that future researchers consult Strauss et al. (2006) and Lezak et al. (2012) for more detailed recommendations of neuropsychological tests that are most appropriate for detecting changes in cognition in PD. It is also recommended that practising neuropsychologists remain informed of the refinement and future changes to the MDS criteria (Goldman et al., 2015), and consult specialized compendiums of neuropsychological tests to ensure the most appropriate tests are administered during standardised assessments of cognition in PD and PD-MCI.

4. **Explore the efficacy of cognitive training and tDCS with varying lengths and frequency of interventions.** This research identified that 12 sessions of cognitive training and 4 sessions of tDCS over 4 weeks led to improvements in cognition, activities of daily living, and quality of life in PD-MCI. However, there is currently no formal consensus regarding the most efficacious parameters of these interventions. Future clinical trials of cognitive training and tDCS need to explore the effects of differing intervention lengths (e.g., 20 to 40 sessions), frequency (e.g., daily or weekly), and intensity (e.g., 20 minutes or 2 hours) to increase our understanding of the effects of these therapies in PD-MCI. Combining cognitive training with tDCS was most efficacious in the current research. Therefore, future studies may wish to explore the effects of a longer intervention (e.g., 12 weeks of cognitive training and tDCS) to examine the potential benefits and feasibility of combining these interventions over an extended period of time.

5. **Explore the efficacy of group-based cognitive training interventions in PD-MCI.** Study 3 involved cognitive training that was completed individually by participants in their homes. However, a number of

participants reported that the training was monotonous and too repetitive. Group-based cognitive training has shown greater efficacy than in-home cognitive training in healthy-older adults (Lampit et al., 2014), and may provide additional benefits (e.g., trainer supervision, social interactions). It is recommended that future studies examine the effects of group-based cognitive training in PD-MCI and include social engagement as a primary outcome (Mor et al., 1995).

6. **Examine the therapeutic effects of tDCS over different cortical sites.** The cortical site of tDCS will influence which cognitive domains are most likely to benefit from stimulation. Study 3 administered tDCS over the left DLPFC which resulted in improvements in executive function, but no improvements in visuospatial abilities. Visuospatial abilities are mediated by the right posterior hemisphere (not the left DLPFC). Future studies may therefore want to examine the effects of tDCS over different cortical sites in PD-MCI, with intention of improving cognitive functions associated with those regions in the brain.

7. **Ensure exposure to interventions is equal across groups.** Participants in the cognitive training + tDCS groups completed a greater number of intervention sessions, compared to the groups that completed interventions independently. Increased exposure to an intervention may therefore produce biased beneficial effects, which compromise the internal validity of results. Researchers need to implement nonpharmacological interventions that are matched for methodological parameters (e.g., intensity, length, time) to ensure any future findings are supported by rigorous empirical design.

8. **Use alternate forms for neuropsychological tests administered at post-intervention and follow up assessments.** In Study 3 the same neuropsychological tests were administered at pre-intervention, post-intervention, and follow up assessments. Using the same tests may result in practice effects during the course of an intervention, which limits the

interpretation of potential therapeutic effects. Future clinical trials should therefore include alternate forms for neuropsychological tests (see Lezak et al., 2012), which eliminate practice effects and maintain standardised assessment of cognitive function at post-intervention and follow up assessments.

9. **Include quality of life and activities of daily living as primary outcomes.** This research provides preliminary evidence to suggest that cognitive training and tDCS may improve activities of daily living and quality of life in PD-MCI. Difficulties with activities of daily living (Rosenthal et al., 2010) and worsened quality of life (van Uem et al., 2016) are well documented in PD, but there is limited evidence to suggest that cognitive training and tDCS can improve functioning in these domains. Future studies need to build upon the findings of Study 3 and explore the potential of these nonpharmacological interventions for improving activities of daily living and quality of life in PD-MCI.

10. **Include neuroimaging data as primary outcomes.** Neuroimaging techniques are uncovering the complex neurobiological processes that are associated with cognitive impairments in PD (e.g., Xu et al., 2016). Using neuroimaging to measure cortical activity pre and post cognitive training and tDCS interventions will provide evidence to indicate which cortical regions are most activated following these interventions, and whether increased cortical activity is associated with improvements on neuropsychological tests. There is also potential for neuroimaging to assist in determining whether stimulation or compensation-focussed interventions produce the greatest adaptive neural plasticity in people with PD-MCI.

11. **Include follow up assessments at 3, 6, and 12 months post-intervention.** Study 3 was the first clinical trial of cognitive training and tDCS to report long-term (12 week) improvements in cognition and quality of life in PD-MCI. Very few studies have included long-term follow up assessments, and it is not known whether the beneficial effects

of these interventions are maintained beyond intervention cessation. It is therefore recommended that future studies build upon the findings from this research and include assessments of cognition, activities of daily living, and quality of life at 3, 6, and 12 months post-intervention.

12. **Explore the efficacy of cognitive training and tDCS among groups of participants at varying stages of PD-MCI and with differing demographic characteristics.** This research explored the effects of cognitive training and tDCS in people identified with PD-MCI at the most liberal cut off (i.e., < 1 SD below normative data). Future studies may want to use a more conservative cut off score (e.g., < 2 SDs below normative data) to examine if cognitive training and tDCS can elicit neural plasticity and improvements in cognitive function in people with more severe cognitive impairments. Future researchers may also wish to explore the effects of these interventions in people with varying levels of education (i.e., varying levels of cognitive reserve), age cohorts, severity of Parkinsonian symptoms, and across the spectrum of the disease course (e.g., de novo to advanced PD).

5.5 Closing Words

It took 150 years from James Parkinson's 'An Essay on the Shaking Palsy' for the development of the first effective therapy for the motor symptoms of Parkinson's Disease (PD) – high-dosage levodopa (Fahn, 2015). It is undeniable that the motor symptoms of PD infiltrate every aspect of a person's life and need to be targeted as the primary symptom of treatment. As described in this thesis, PD is now recognised as a disorder that encompasses many motor and non-motor symptoms, including mild cognitive impairment.

Over the past 5 years, the scientific community has increased their focus on nonpharmacological therapies for cognitive impairments in PD and to complement the pharmacological benefits of levodopa for motor symptoms. This thesis explored the therapeutic potential of nonpharmacological interventions for improving cognition and quality of life for people with PD. It is hoped that the findings presented in this thesis will add to and expand the current evidence base in support of cognitive training and transcranial direct current stimulation for mild cognitive impairment in PD, and motivate fellow researchers to continue to explore the potential of these interventions to improve the quality of life for the many millions of people living with PD.

To close this thesis, I would like to extend the most whole hearted thank you to the people with Parkinson's who volunteered their time to contribute to this research. This research would not exist if it wasn't for the altruistic effort contributed by each of you and I am thankful for being welcomed into your lives and your communities.

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Appendices

Appendix A

To Whom It May Concern

I, Blake Justin Lawrence, contributed to the study design, recruiting participants, conducting neuropsychological assessments, analysing the data, writing the initial manuscript, and editing the final manuscript of the publication entitled '*Lawrence, BJ, et al. Prevalence and Subtypes of Mild Cognitive Impairment in Parkinson's Disease. Scientific Reports, In Press, (2016).*'

Candidate signature: …….

I, as a Co-Author, endorse that this level of contribution by the candidate indicated above is appropriate.

Co-Author 1: A/Prof. Natalie Gasson ……. Signature: ……

Co-Author 2: A/Prof. Andrea Loftus ……. Signature: ……

Appendix B

Sources of Normative Data for Study 1 (Chapter 2)

Cognitive Domain	Neuropsychological Test	Norm Reference
Executive Function	Stockings of Cambridge	Cambridge Neuropsychological Test of Automated Batteries (CANTAB™) Software (http://www.cambridgecognition.com/)
	Controlled Oral Word Association	Tombaugh, T. N., & Hubiey, A. M. (1997). The 60-item Boston Naming Test: Norms for cognitively intact adults aged 25 to 88 years. *Journal of Clinical and Experimental Neuropsychology, 19*, 922-932. doi:10.1080/01688639708403773
Attention / Working Memory	Letter-Number Sequencing	Wechsler, D. (2008). Wechsler Adult Intelligence Scale–Fourth Edition (WAIS–IV). *San Antonio, TX: NCS Pearson*
	Stroop (Colour-Word) Test	Fisher, L. M., Freed, D. M., & Corkin, S. (1990). Stroop Color-Word Test performance in patients with Alzheimer's disease. *Journal of Clinical and Experimental Neuropsychology, 12*, 745-758. doi:10.1080/01688639008401016
Memory	Hopkins Verbal Learning Test – Revised	Brandt, J., & Benedict, R. H. (2001). *Hopkins Verbal Learning Test-Revised: Professional Manual*. Lutz, FL: Psychological Assessment Resources. Hester, R. L., Kinsella, G. J., Ong, B., & Turner, M. (2004). Hopkins verbal learning test: Normative data for older Australian adults. *Australian Psychologist, 39*, 251-255. doi:10.1080/00050060412331295063
	Paragraph Recall	Wilson, B., Cockburn, J., Baddeley, A., & Hiorns, R. (1989). The development and validation of a test battery for detecting and monitoring everyday memory problems. *Journal of Clinical and Experimental Neuropsychology, 11*, 855-870. doi:10.1080/01688638908400940 Strauss, E., Sherman, E., & Spreen, O. (2006). *A compendium of neuropsychological tests: Administration, norms, and commentary*. UK: Oxford University Press.

Visuospatial	Judgement of Line Orientation	Glamser, F. D., & Turner, R. W. (1995). Youth sport participation and associated sex differences on a measure of spatial ability. *Perceptual and motor skills, 81*, 1099-1105. doi:10.2466/pms.1995.81.3f.1099 Ska, B., Poissant, A., & Joanette, Y. (1990). Line orientation judgment in normal elderly and subjects with dementia of Alzheimer's type. *Journal of Clinical and Experimental Neuropsychology, 12*, 695-702. doi:10.1080/01688639008401012
	Hooper Visual Organisation Test	Tamkin, A. S., & Jacobsen, R. (1984). Age-related norms for the Hooper Visual Organization Test. *Journal of clinical psychology, 40*, 1459-1463. doi:10.1002/1097-4679(198411)40:6<1459::AID-JCLP2270400633>3.0.CO;2-3
Language	Boston Naming Test – Short	Fastenau, P. S., Denburg, N. L., & Mauer, B. A. (1998). Parallel short forms for the Boston Naming Test: Psychometric properties and norms for older adults. *Journal of Clinical and Experimental Neuropsychology, 20*, 828-834. doi:10.1076/jcen.20.6.828.1105
	Similarities	Wechsler, D. (2008). Wechsler Adult Intelligence Scale–Fourth Edition (WAIS–IV). *San Antonio, TX: NCS Pearson*.

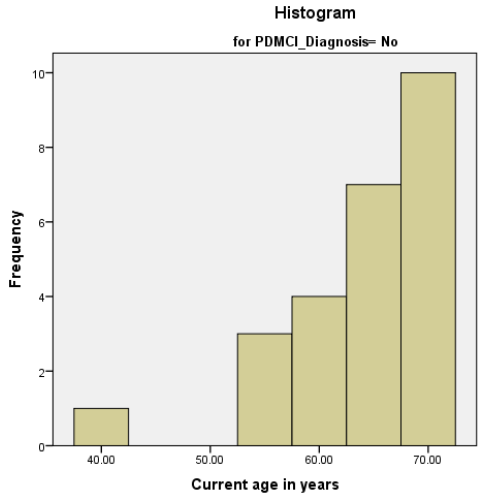
Appendix C

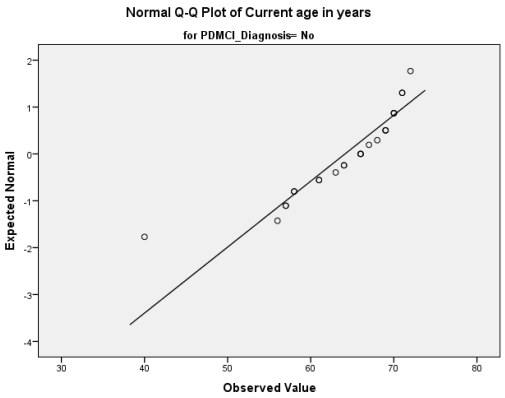
Normality output for Study 1 variables.

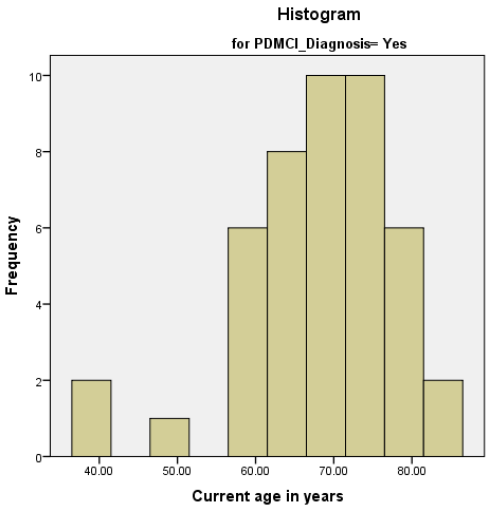
Tests of Normality

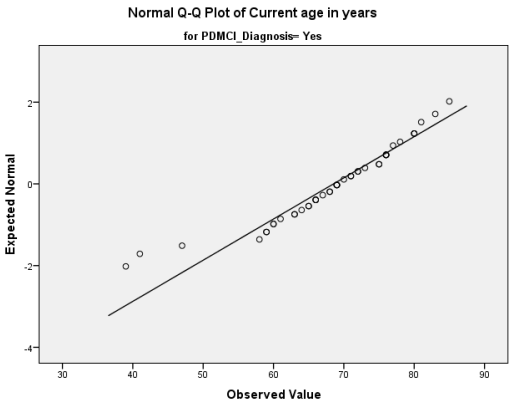
		Kolmogorov-Smirnov[a]			Shapiro-Wilk		
	PDMCI Diagnosis	Statistic	df	Sig.	Statistic	df	Sig.
Current age in years	No	.164	25	.080	.842	25	.001
	Yes	.094	45	.200*	.927	45	.007
Years of education from AUSNART	No	.166	25	.072	.922	25	.057
	Yes	.119	45	.120	.972	45	.337
WAIS Estimate of premorbid VIQ	No	.348	25	.000	.418	25	.000
	Yes	.143	45	.022	.901	45	.001
Years of Disease Duration	No	.173	25	.053	.812	25	.000
	Yes	.178	45	.001	.913	45	.002
Levodopa Equivalent Dose	No	.146	25	.176	.937	25	.126
	Yes	.211	45	.000	.853	45	.000
UPDRS ADL SI	No	.168	25	.068	.920	25	.050
	Yes	.104	45	.200*	.964	45	.178
TISC Total Score	No	.109	25	.200*	.975	25	.772
	Yes	.222	45	.000	.899	45	.001
MMSE Serial 7s total	No	.139	25	.200*	.918	25	.047
	Yes	.177	45	.001	.874	45	.000
Word Fluency total	No	.141	25	.200*	.957	25	.358
	Yes	.124	45	.078	.955	45	.079
SOC Problems solved in minimum moves	No	.166	25	.075	.906	25	.025
	Yes	.120	45	.103	.961	45	.139
Letter-Number Sequencing	No	.135	25	.200*	.938	25	.136
	Yes	.204	45	.000	.841	45	.000
Letter-Number Sequencing	No	.135	25	.200*	.938	25	.136
	Yes	.204	45	.000	.841	45	.000
Stroop Test total score	No	.131	25	.200*	.932	25	.097
	Yes	.124	45	.078	.954	45	.071
HVLT total of 3 trials	No	.176	25	.045	.947	25	.215
	Yes	.093	45	.200*	.970	45	.297
Paragraph recall raw score	No	.167	25	.069	.871	25	.004
	Yes	.135	45	.038	.967	45	.231
Boston Naming Test Total Score	No	.322	25	.000	.749	25	.000
	Yes	.204	45	.000	.859	45	.000
Similarities Total Score	No	.162	25	.088	.961	25	.428
	Yes	.146	45	.017	.949	45	.045
Similarities Scale Score	No	.178	25	.040	.944	25	.184
	Yes	.168	45	.003	.948	45	.044
Judgment of line orientation total	No	.191	25	.020	.868	25	.004
	Yes	.166	45	.003	.856	45	.000
Hooper's Visual Organisation Test Total	No	.175	25	.048	.948	25	.220
	Yes	.100	45	.200*	.977	45	.504

Variable = Age









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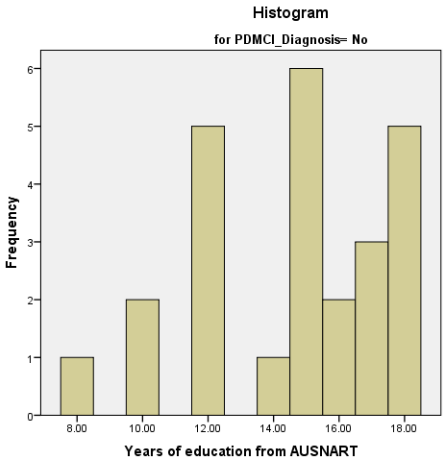
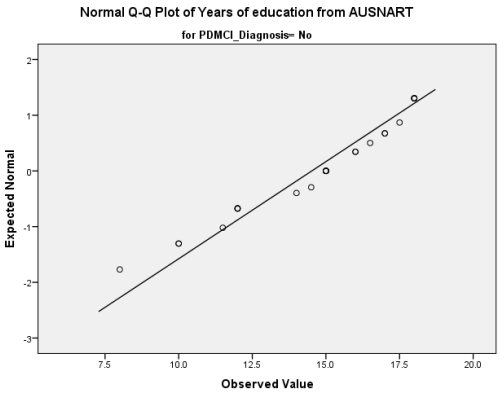
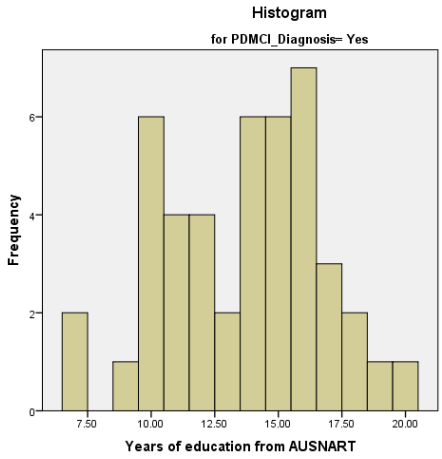
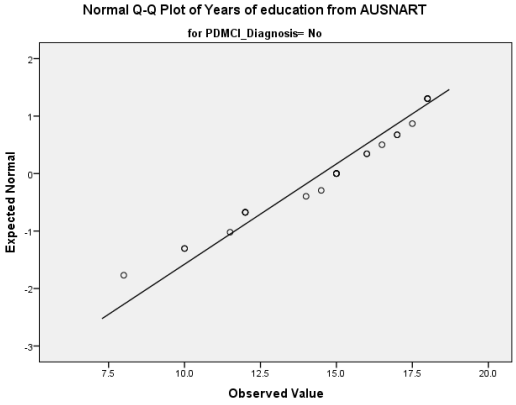
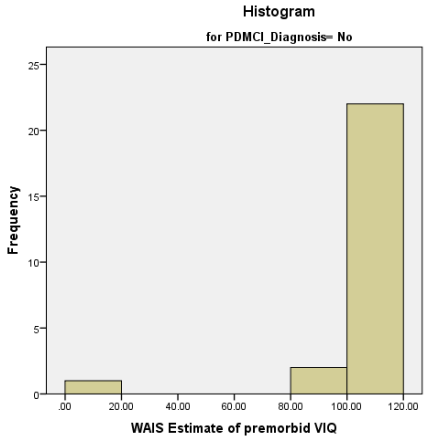


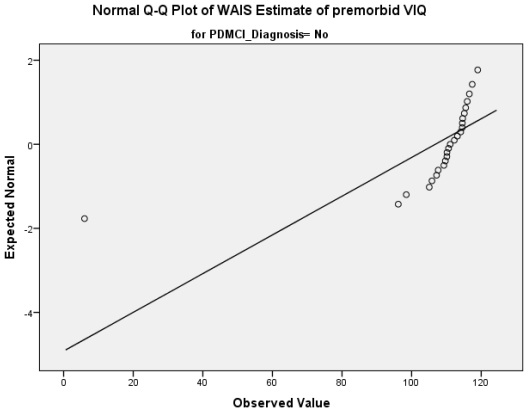


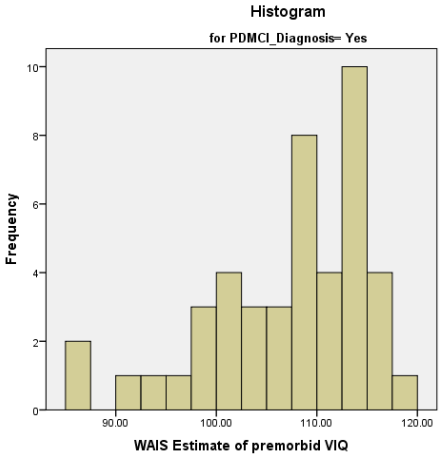


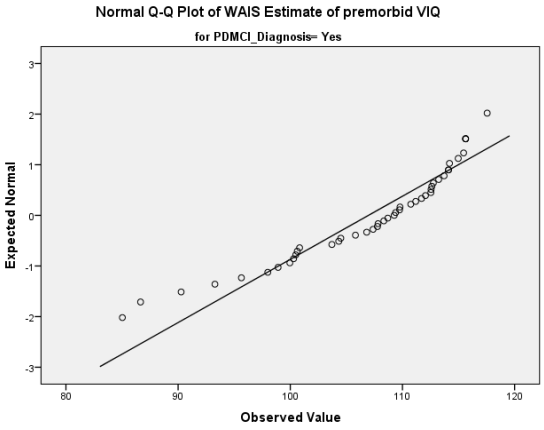


Variable = Premorbid IQ

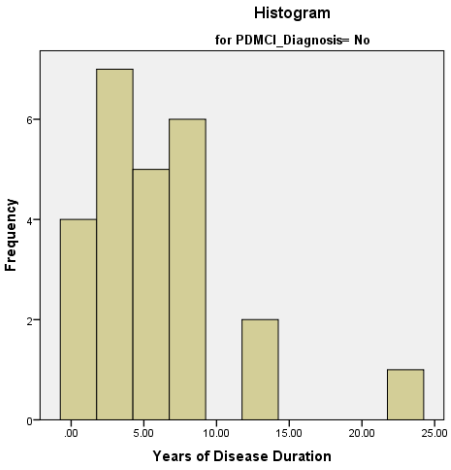


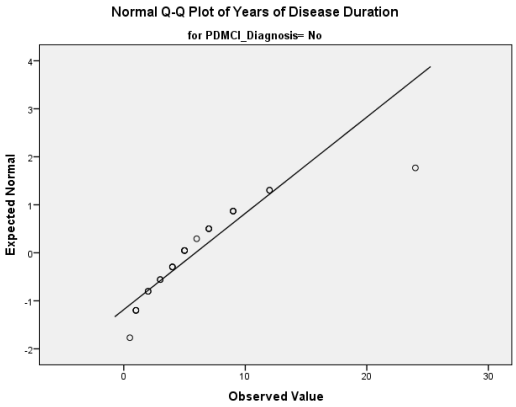


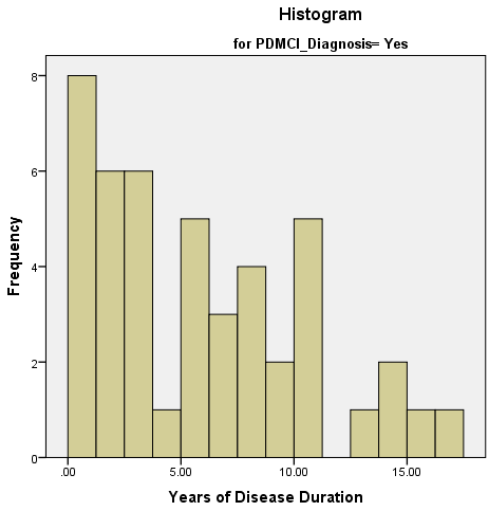


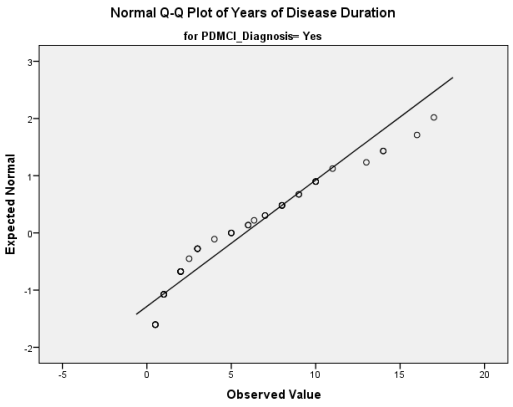


Variable = Years of Disease Duration









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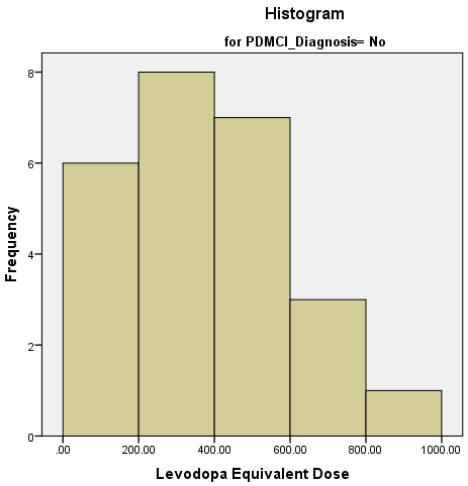

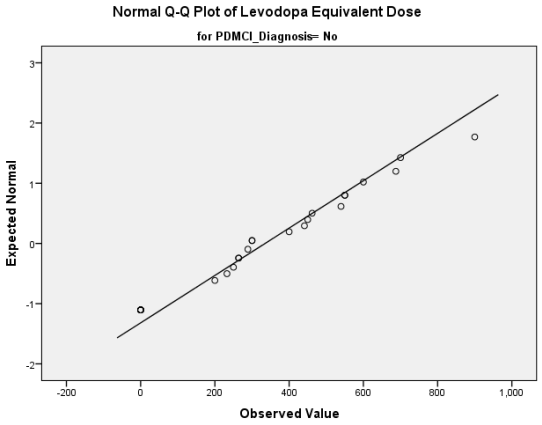

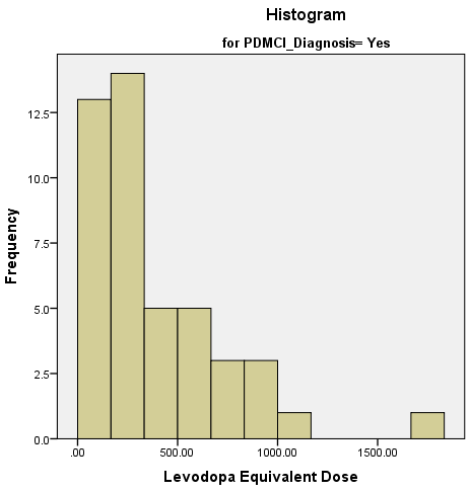

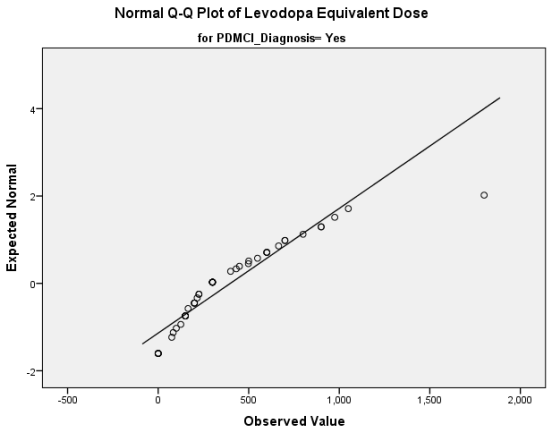

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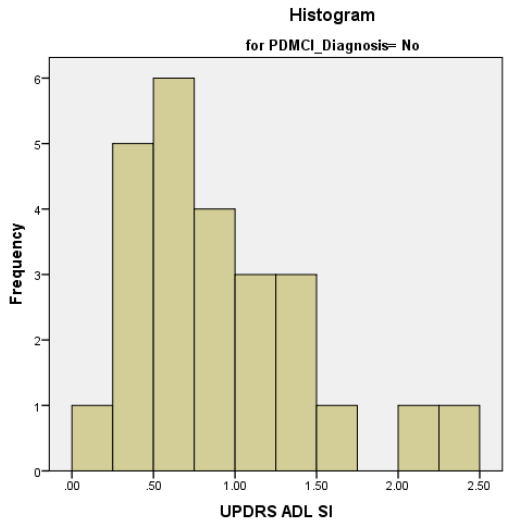

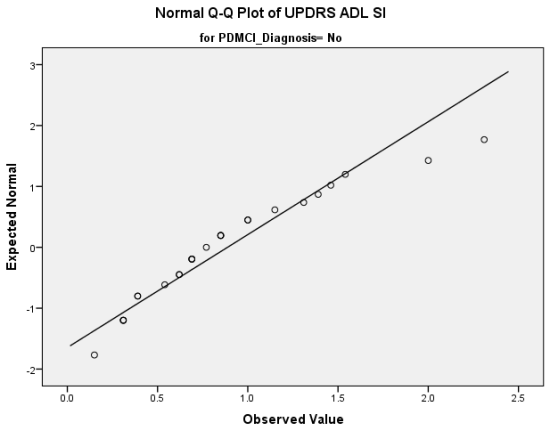

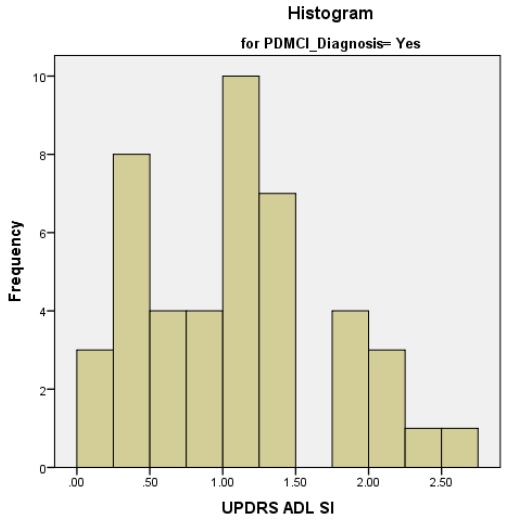

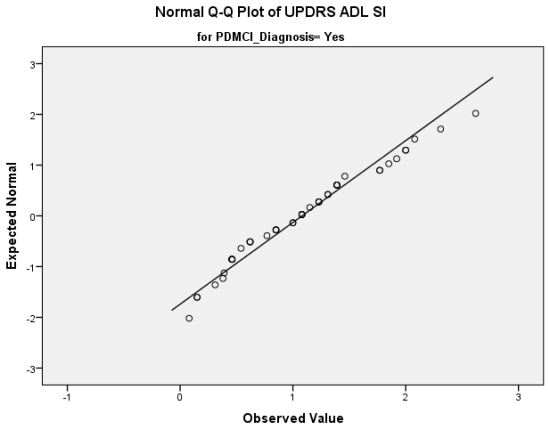

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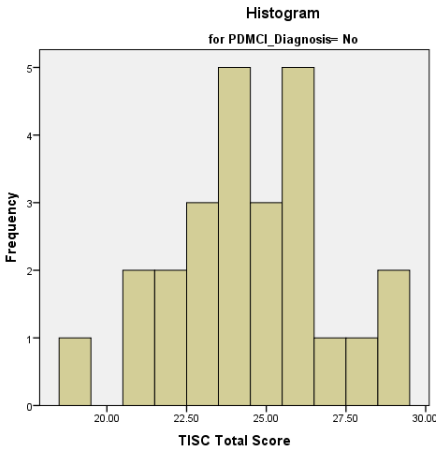

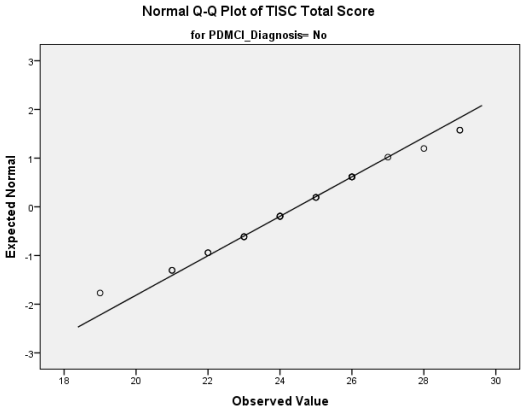

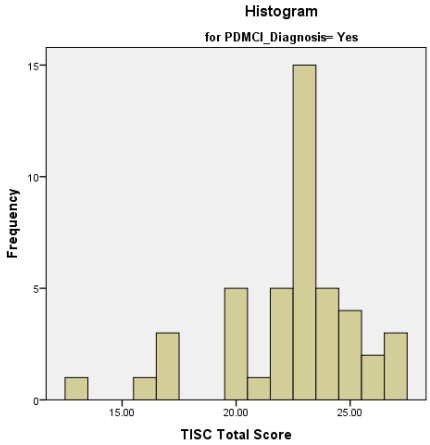

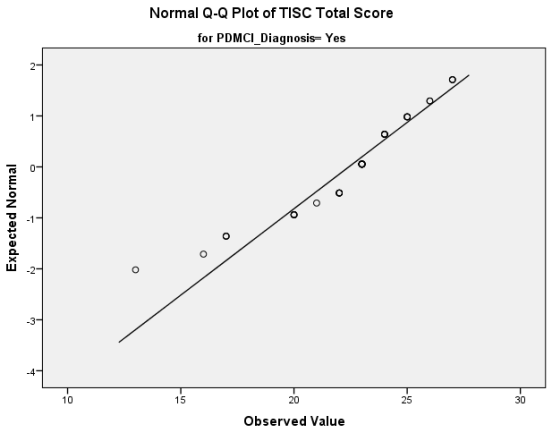

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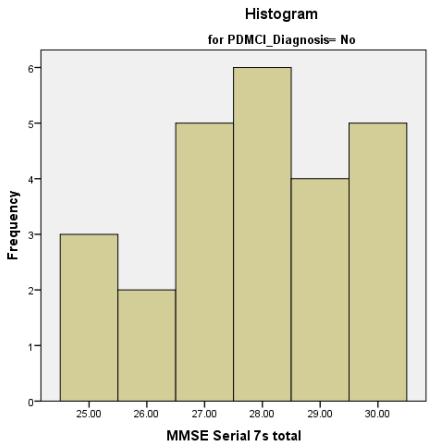

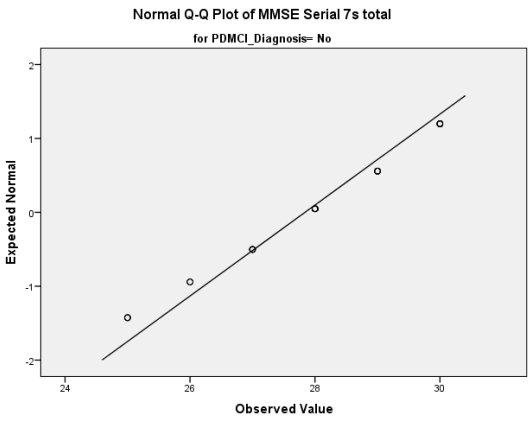

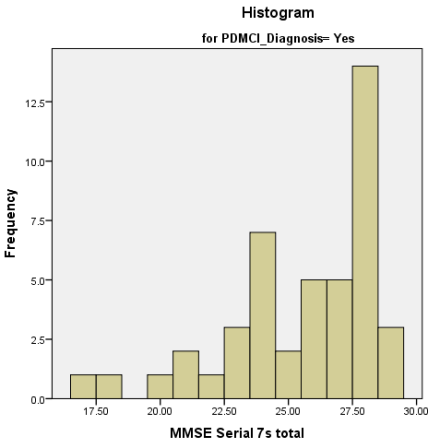

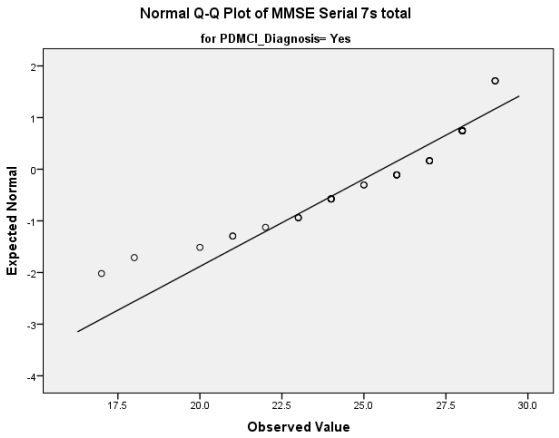

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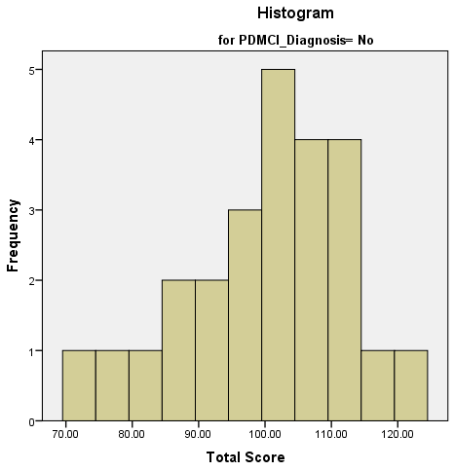

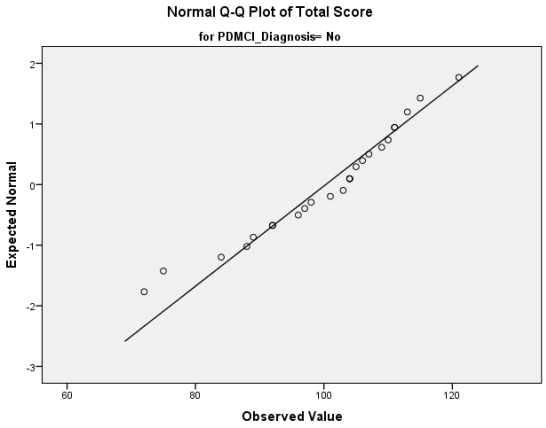

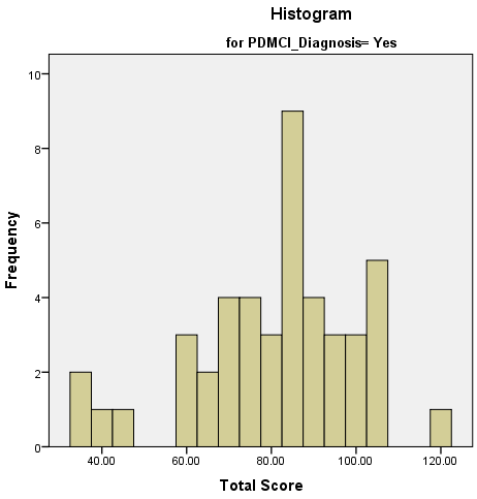

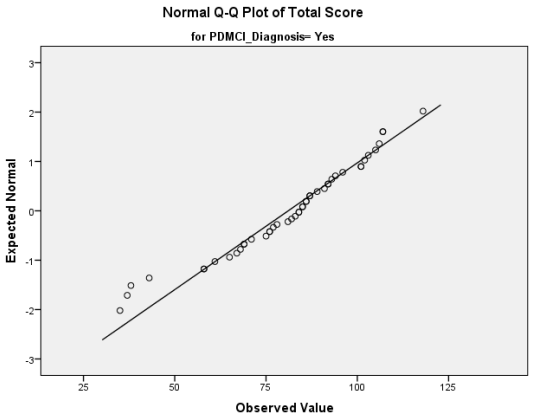

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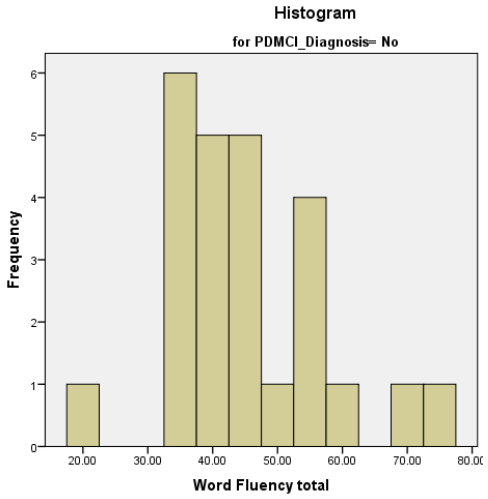

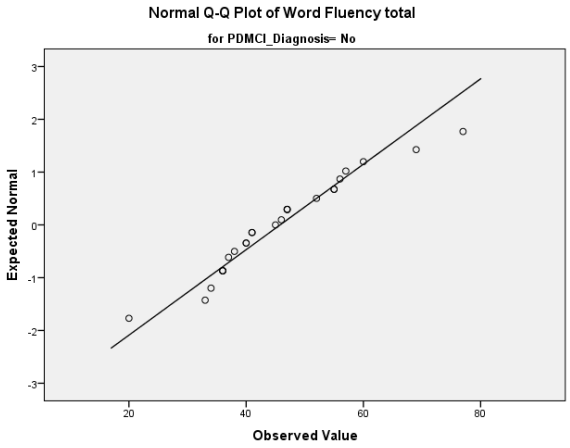

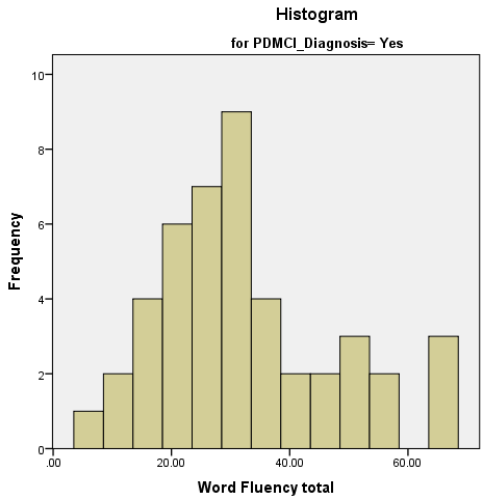

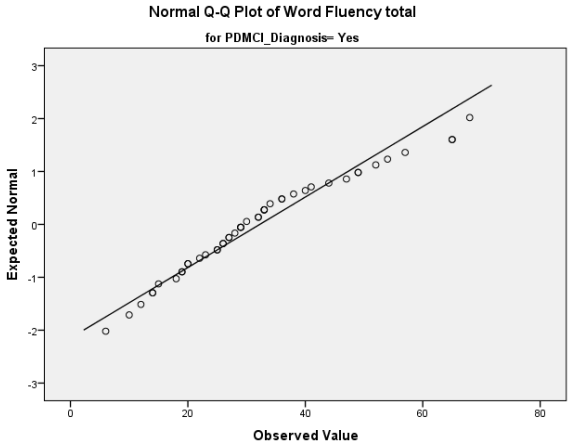

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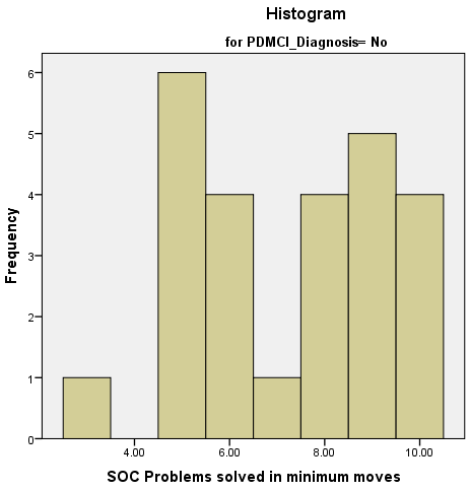

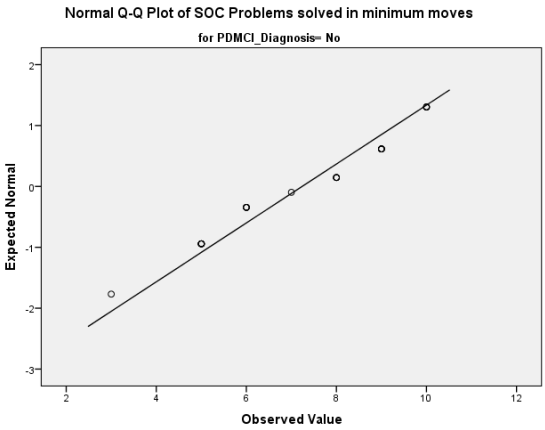

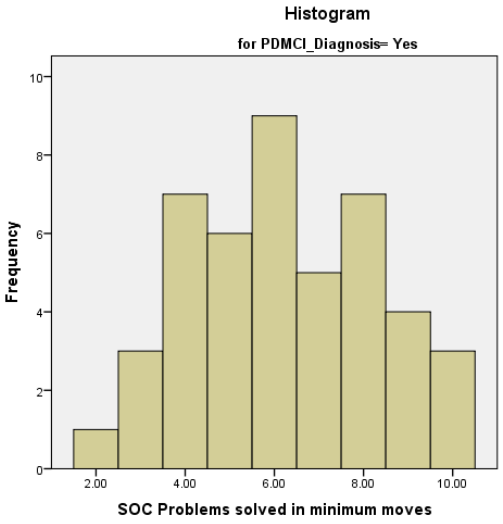

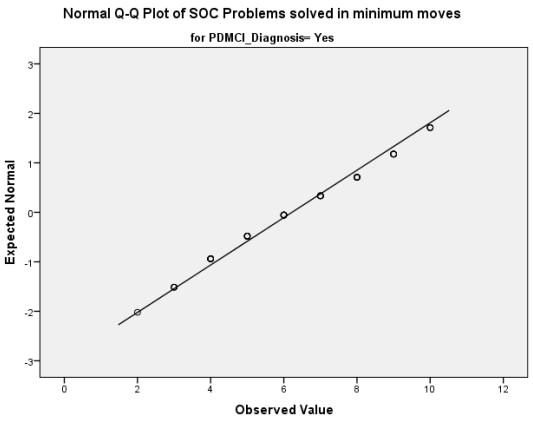

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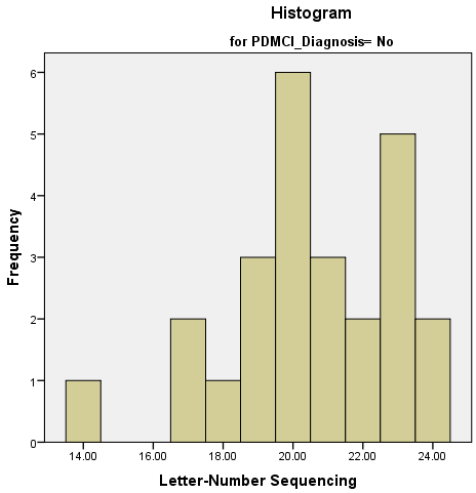
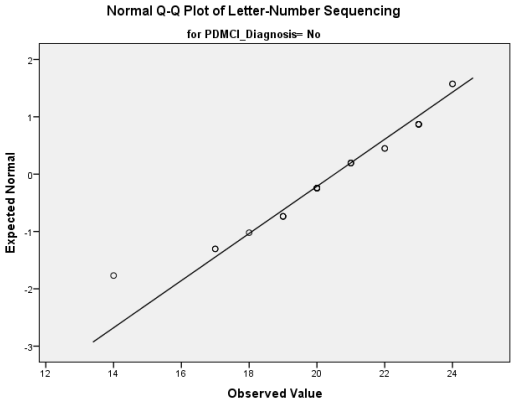
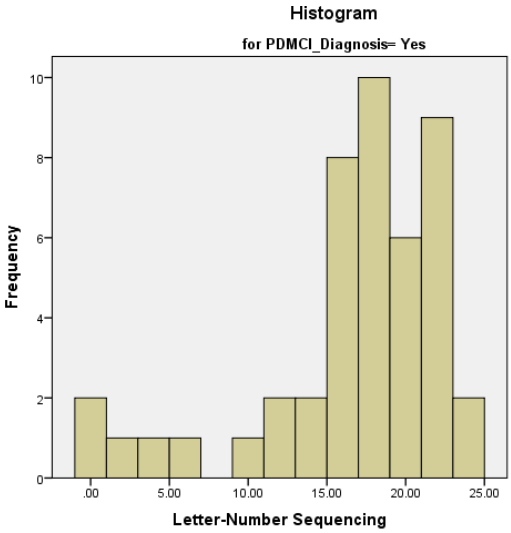
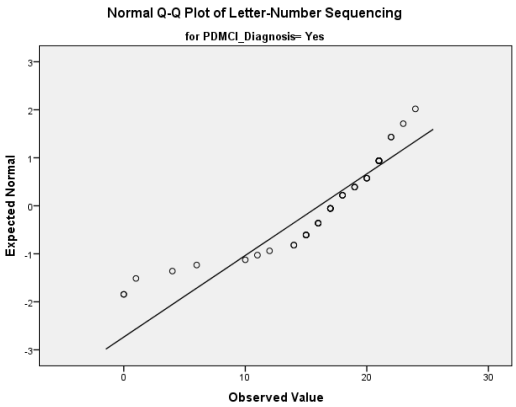
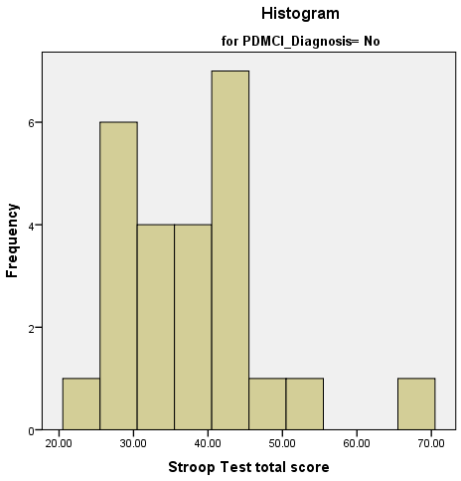


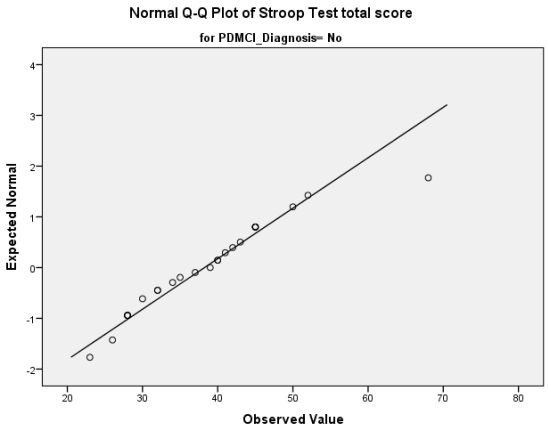


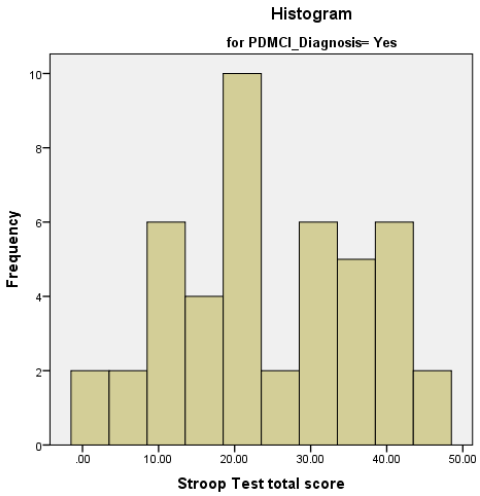


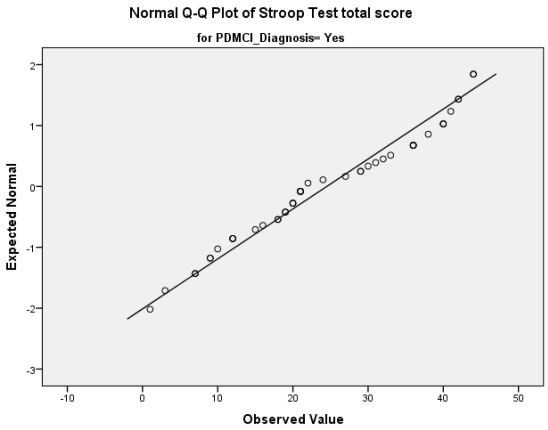


Variable = Stroop Test









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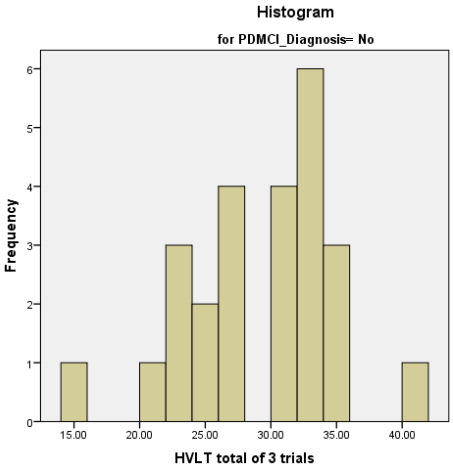
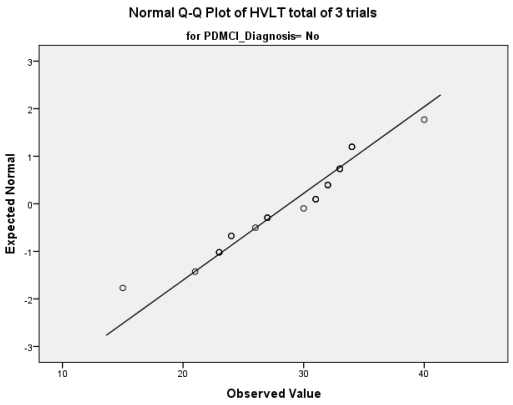
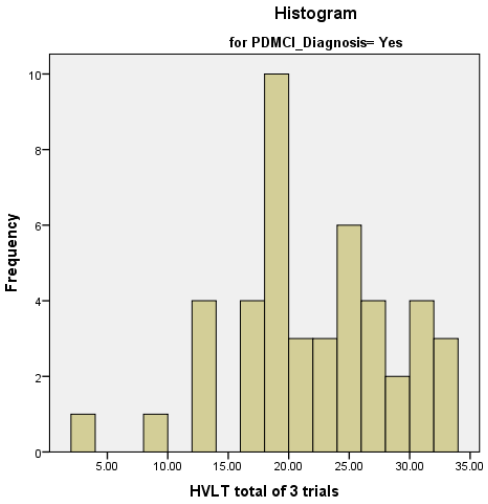
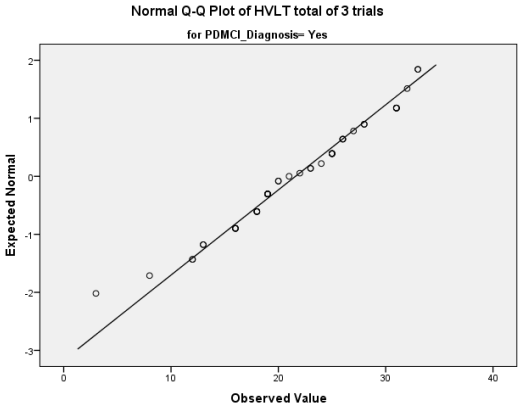
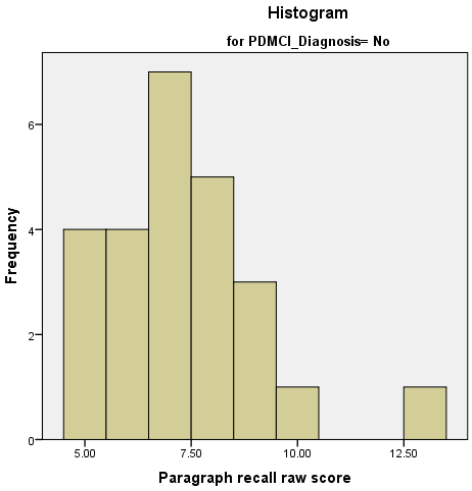


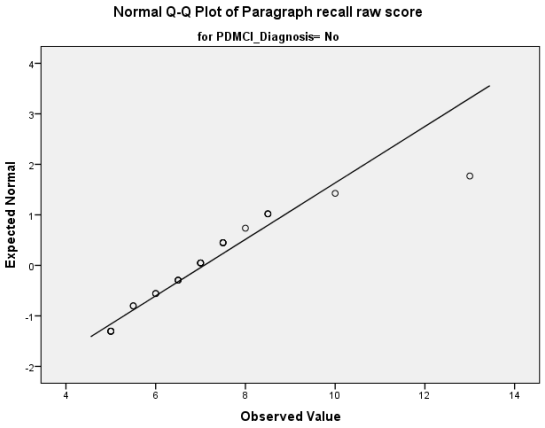


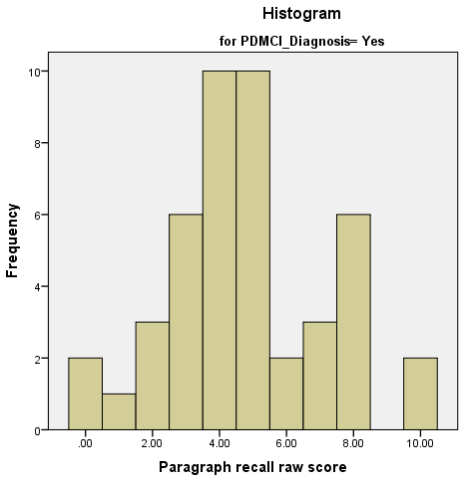


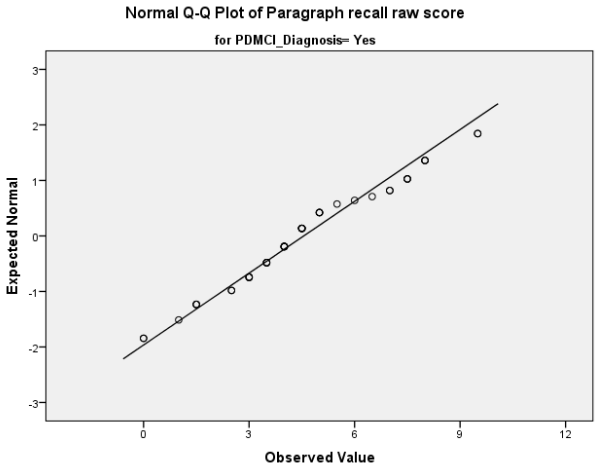


Variable = Paragraph Recall

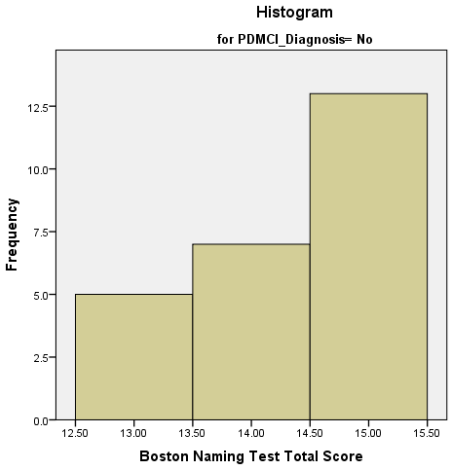


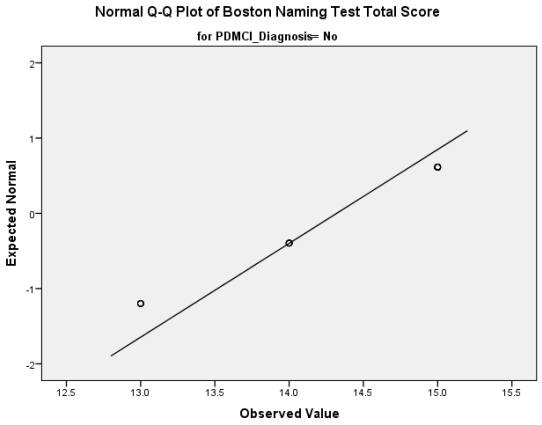


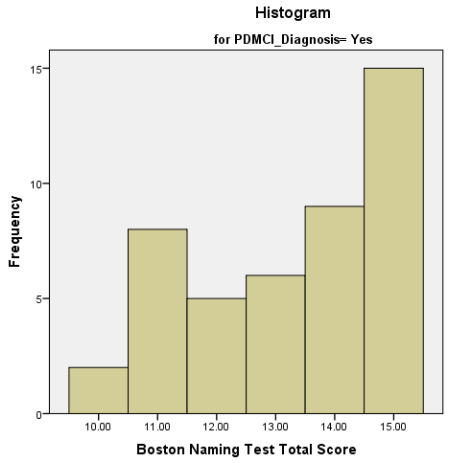


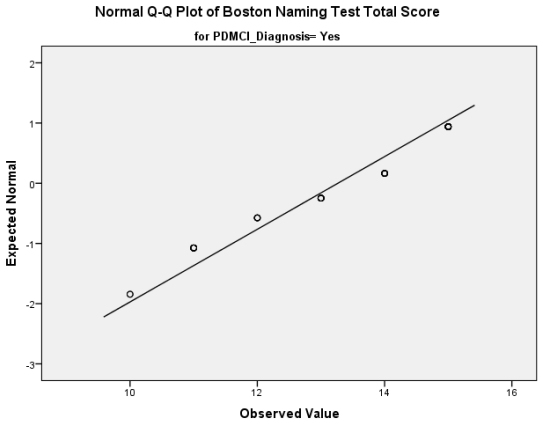


Variable = BNT









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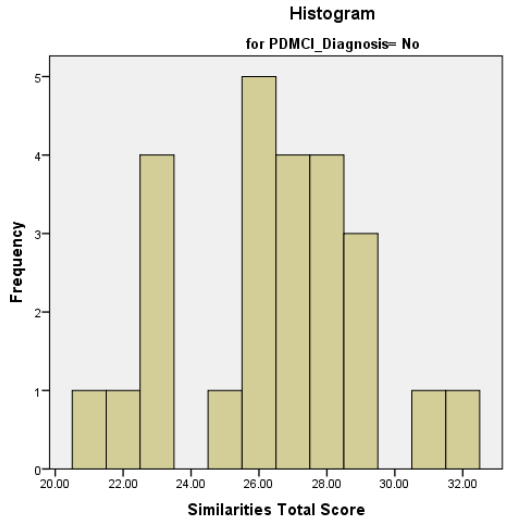

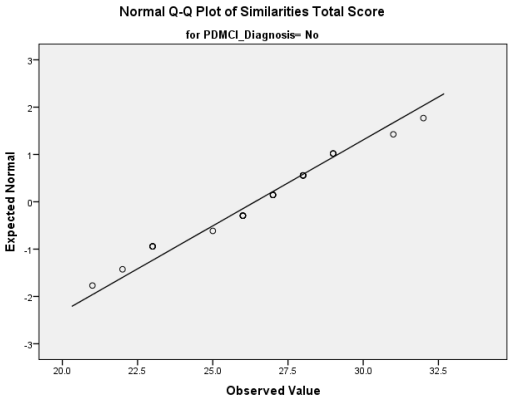

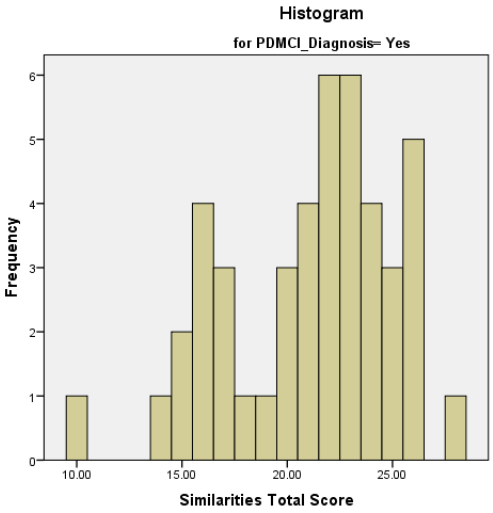

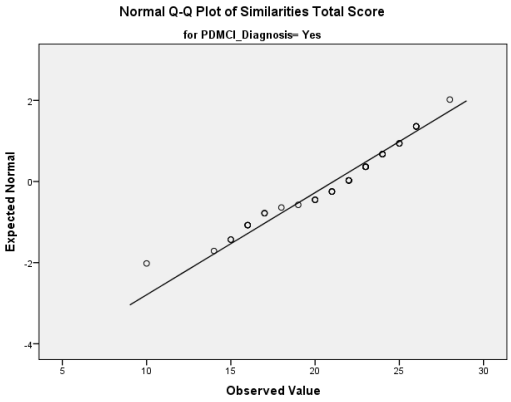

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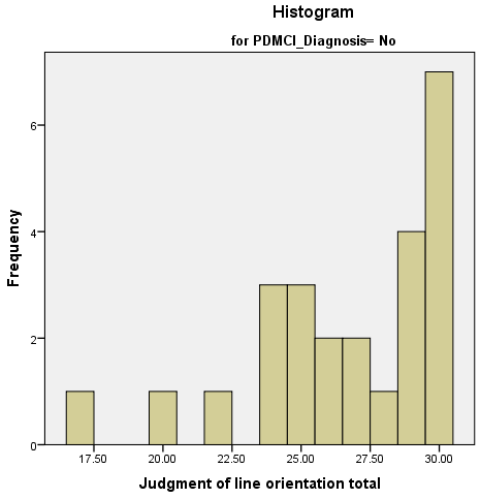

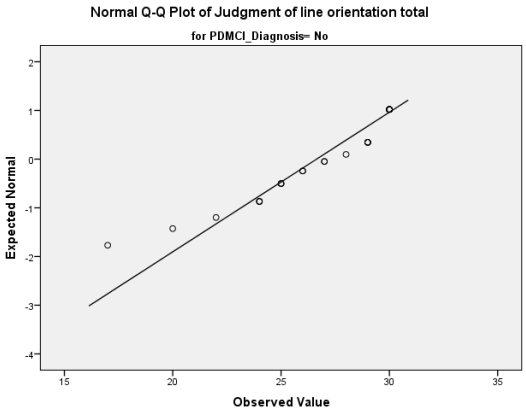

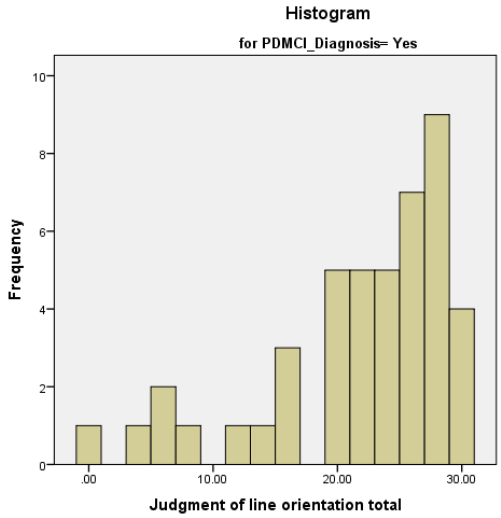

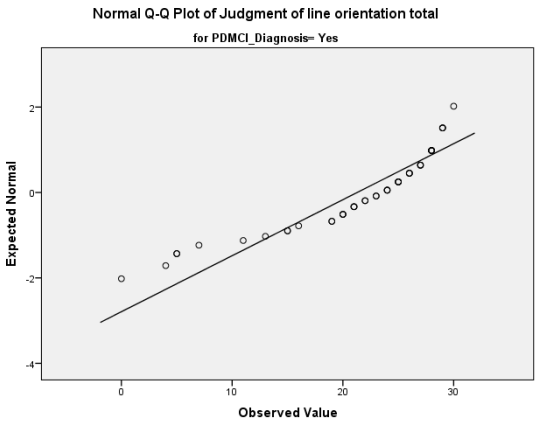

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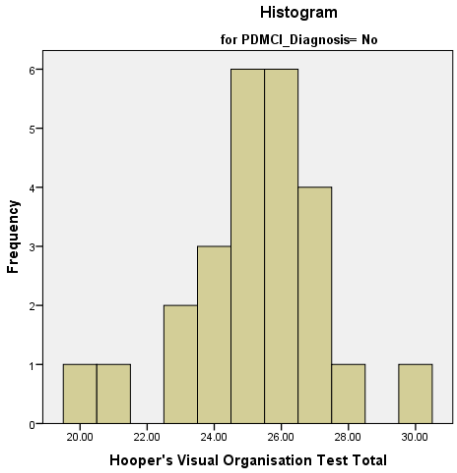

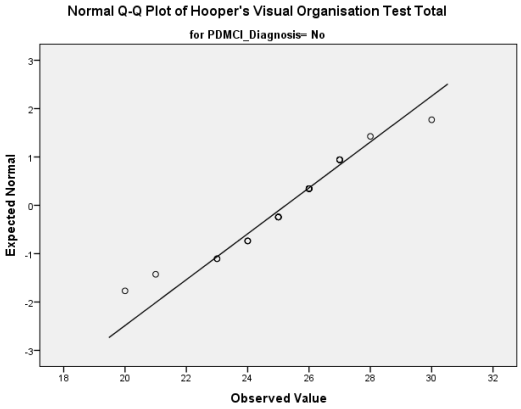

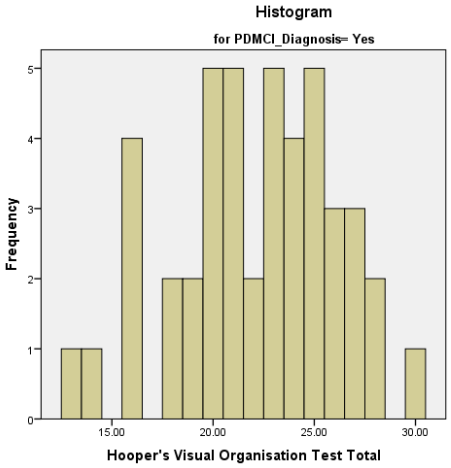

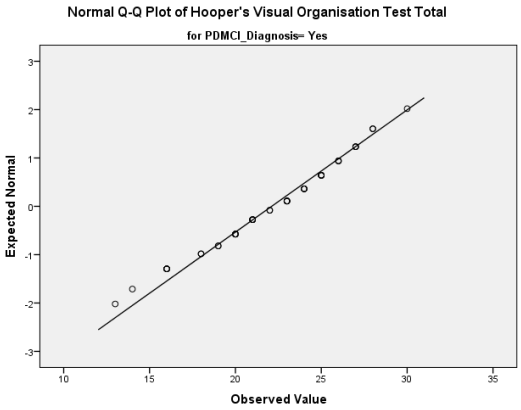

Appendix D

Normality assumption results for Study 3 variables.

Tests of Normality

	Kolmogorov-Smirnov[a]			Shapiro-Wilk		
	Statistic	df	Sig.	Statistic	df	Sig.
Word Fluency total	.134	38	.084	.949	38	.080
Word Fluency total	.129	38	.114	.950	38	.090
Word Fluency total	.101	38	.200*	.983	38	.814

*. This is a lower bound of the true significance.

a. Lilliefors Significance Correction

Tests of Normality

		Kolmogorov-Smirnov[a]			Shapiro-Wilk		
	Time	Statistic	df	Sig.	Statistic	df	Sig.
SOC Problems solved in minimum moves	Pre-Intervention	.126	42	.090	.966	42	.239
	Post-Intervention	.140	37	.066	.943	37	.059
	Follow-up	.182	34	.006	.945	34	.086

a. Lilliefors Significance Correction

Tests of Normality

	Kolmogorov-Smirnov[a]			Shapiro-Wilk		
	Statistic	df	Sig.	Statistic	df	Sig.
Letter-Number Sequencing	.186	38	.002	.853	38	.000
Letter-Number Sequencing	.265	38	.000	.805	38	.000
Letter-Number Sequencing	.153	38	.024	.870	38	.000

a. Lilliefors Significance Correction

Tests of Normality

	Kolmogorov-Smirnov[a]			Shapiro-Wilk		
	Statistic	df	Sig.	Statistic	df	Sig.
Stroop Test total score	.171	38	.007	.926	38	.015
Stroop Test total score	.074	38	.200*	.987	38	.933
Stroop Test total score	.066	38	.200*	.987	38	.922

*. This is a lower bound of the true significance.

a. Lilliefors Significance Correction

Tests of Normality

	Kolmogorov-Smirnov[a]			Shapiro-Wilk		
	Statistic	df	Sig.	Statistic	df	Sig.
HVLT total of 3 trials	.096	38	.200*	.957	38	.156
HVLT total of 3 trials	.133	38	.087	.919	38	.009
HVLT total of 3 trials	.183	38	.003	.925	38	.014

*. This is a lower bound of the true significance.

a. Lilliefors Significance Correction

Tests of Normality

	Kolmogorov-Smirnov[a]			Shapiro-Wilk		
	Statistic	df	Sig.	Statistic	df	Sig.
Paragraph recall raw score	.129	38	.114	.972	38	.454
Paragraph recall raw score	.145	38	.041	.967	38	.314
Paragraph recall raw score	.165	38	.010	.936	38	.032

a. Lilliefors Significance Correction

Tests of Normality

	Kolmogorov-Smirnov[a]			Shapiro-Wilk		
	Statistic	df	Sig.	Statistic	df	Sig.
Boston Naming Test Total Score	.207	38	.000	.863	38	.000
Boston Naming Test Total Score	.263	38	.000	.783	38	.000
Boston Naming Test Total Score	.217	38	.000	.835	38	.000

a. Lilliefors Significance Correction

Tests of Normality

	Kolmogorov-Smirnov[a]			Shapiro-Wilk		
	Statistic	df	Sig.	Statistic	df	Sig.
Similarities Total Score	.123	38	.160	.956	38	.142
Similarities Total Score	.151	38	.030	.958	38	.169
Similarities Total Score	.180	38	.003	.929	38	.018

a. Lilliefors Significance Correction

Tests of Normality

	Kolmogorov-Smirnov[a]			Shapiro-Wilk		
	Statistic	df	Sig.	Statistic	df	Sig.
Judgment of line orientation total	.151	38	.030	.877	38	.001
Judgment of line orientation total	.200	38	.001	.893	38	.002
Judgment of line orientation total	.168	38	.008	.843	38	.000

a. Lilliefors Significance Correction

Tests of Normality

	Kolmogorov-Smirnov[a]			Shapiro-Wilk		
	Statistic	df	Sig.	Statistic	df	Sig.
Hooper's Visual Organisation Test Total	.105	38	.200*	.972	38	.437
Hooper's Visual Organisation Test Total	.152	38	.028	.926	38	.015
Hooper's Visual Organisation Test Total	.109	38	.200*	.941	38	.045

*. This is a lower bound of the true significance.

a. Lilliefors Significance Correction

Tests of Normality

	Kolmogorov-Smirnov[a]			Shapiro-Wilk		
	Statistic	df	Sig.	Statistic	df	Sig.
MMSE Serial 7s total	.214	38	.000	.883	38	.001
MMSE Serial 7s total	.166	38	.010	.907	38	.004
MMSE Serial 7s total	.174	38	.005	.888	38	.001

a. Lilliefors Significance Correction

Tests of Normality

	Kolmogorov-Smirnov[a]			Shapiro-Wilk		
	Statistic	df	Sig.	Statistic	df	Sig.
Total Score	.100	38	.200*	.966	38	.305
PDCRS Total Score	.099	38	.200*	.972	38	.445
Total Score	.086	38	.200*	.950	38	.090

*. This is a lower bound of the true significance.

a. Lilliefors Significance Correction

Tests of Normality

	Kolmogorov-Smirnov[a]			Shapiro-Wilk		
	Statistic	df	Sig.	Statistic	df	Sig.
UPDRS ADL SI	.108	38	.200*	.955	38	.129
UPDRS ADL SI	.167	38	.009	.887	38	.001
UPDRS ADL SI	.144	38	.045	.889	38	.001

*. This is a lower bound of the true significance.

a. Lilliefors Significance Correction

Tests of Normality

	Kolmogorov-Smirnov[a]			Shapiro-Wilk		
	Statistic	df	Sig.	Statistic	df	Sig.
PDQ39 - Summary index mean sub total	.149	30	.087	.928	30	.045
PDQ39 - Summary index mean sub total	.130	30	.200*	.929	30	.047
PDQ39 - Summary index mean sub total	.115	30	.200*	.930	30	.049

*. This is a lower bound of the true significance.

a. Lilliefors Significance Correction

Appendix E

Pre-intervention neuropsychological test results for intervention groups

		Standard CT		Tailored CT		tDCS	
Domain	Outcome	*M*	*SD*	*M*	*SD*	*M*	*SD*
EF	COWAT	38.86	14.98	32.43	17.89	30.86	17.39
	SOC	7.85	1.07	6.43	2.51	5.42	1.27
Atten.WM	LNS	18.86	2.41	17.86	4.60	14.71	6.75
	Stroop Test	34.29	8.38	31.43	11.83	20	8.49
Memory	HVLT	22.14	6.52	22.86	6.41	19.42	9.25
	Paragraph Recall	5	2.36	5.64	2.36	4	2.40
Language	BNT	14.14	1.86	13.14	1.35	12.57	1.13
	Similarities	21.71	3.50	22.29	3.45	22.57	3.16
VS	JLO	24.57	2.94	20.14	4.41	21.43	8.44
	HVOT	24.57	4.08	20.29	4.54	21	3.87
Global	MMSE	26.29	2.14	25.86	3.13	24.14	1.77
	PD-CRS	89.57	12.08	88.29	15.82	72.57	19.03
ADL	UPDRS-II	.95	.83	.68	.34	1.27	.59
QOL	PDQ-39	23.50	11.35	18.89	9.82	23.62	11.93
		Standard CT + tDCS		Tailored CT + tDCS		Control	
Domain	Outcome	*M*	*SD*	*M*	*SD*	*M*	*SD*
EF	COWAT	37.71	10.66	32.14	9.96	30.14	16.65
	SOC	7.43	1.51	5.29	1.11	6	3.06
Atten.WM	LNS	18.42	2.82	17.43	3.60	14.29	7.04
	Stroop Test	23.14	9.46	28.57	11.97	18.57	10.01
Memory	HVLT	27.71	3.25	21.29	2.98	20.29	6.87
	Paragraph Recall	6	2.24	3.21	1.55	4.07	2.59
Language	BNT	13.29	1.70	14	1.53	12.43	2.15
	Similarities	21.86	2.41	23.14	3.85	18.43	2.70
VS	JLO	23.86	5.76	23.14	8.25	20.14	8.53
	HVOT	23.43	3.69	21.86	3.81	23.57	2.37
Global	MMSE	27.86	.69	26.71	2.36	24.71	2.63
	PD-CRS	90	13.22	86.14	15.46	74.14	23.23
ADL	UPDRS-II	1	.52	1.17	.61	1.17	.75
QOL	PDQ-39	20.64	19.97	26.73	17.05	24.09	16.50

Appendix F

Post-intervention neuropsychological test results for intervention groups

		Standard CT		Tailored CT		tDCS	
Domain	Outcome	*M*	*SD*	*M*	*SD*	*M*	*SD*
EF	COWAT	44.14	12.28	34.71	13.14	36	16.29
	SOC	6.43	2.70	5.43	3.05	5.57	2.88
Atten.WM	LNS	18.71	4.68	19	4.16	15.86	6.82
	Stroop Test	36.57	10.13	34.71	12.89	26.29	12.57
Memory	HVLT	27	6.73	25.29	7.52	24.43	7.18
	Paragraph Recall	6.36	2.46	7.36	3.78	6.29	2.20
Language	BNT	13.86	1.07	13.86	1.35	13.71	1.98
	Similarities	23.14	3.19	22.14	3.29	23.57	2.64
VS	JLO	23.86	4.30	22.86	4.49	22.57	5.77
	HVOT	25.19	3.86	23.14	4.67	22.43	4.58
Global	MMSE	26.14	2.19	27.28	3.40	25.86	2.27
	PD-CRS	96.29	12.89	97	24.39	82.86	19.39
ADL	UPDRS-II	.73	.80	.80	.43	1.06	.71
QOL	PDQ-39	22.30	10.08	17.38	13.93	21.28	13.77
		Standard CT + tDCS		Tailored CT + tDCS		Control	
Domain	Outcome	*M*	*SD*	*M*	*SD*	*M*	*SD*
EF	COWAT	46.14	5.24	36.29	9.12	27.42	10.71
	SOC	8.43	3.99	7	2.24	5.57	4.20
Atten.WM	LNS	19	2.45	18.43	2.07	14.71	7.09
	Stroop Test	29.14	9.28	29.29	8.12	18.14	9.14
Memory	HVLT	29.71	3.94	25.14	3.48	22.43	7.41
	Paragraph Recall	8.21	1.50	5.71	1.78	4.07	1.95
Language	BNT	14.43	.79	14.29	1.11	13	1.92
	Similarities	23.86	1.46	25.57	3.91	19.14	2.34
VS	JLO	25.57	5.03	23.29	6.68	19.86	9.19
	HVOT	24.71	3.04	24.43	3.60	23.86	2.67
Global	MMSE	27.71	1.60	26.86	1.35	23.71	2.81
	PD-CRS	101.71	12.23	94.43	14.01	75.14	18.73
ADL	UPDRS-II	.62	.56	.97	.52	1.25	1.02
QOL	PDQ-39	15.62	10.36	27.21	14.05	20.34	21.57

Appendix G

Follow-up neuropsychological test results for intervention groups

		Standard CT		Tailored CT		tDCS	
Domain	Outcome	*M*	*SD*	*M*	*SD*	*M*	*SD*
EF	COWAT	20.72	7.66	31.86	25.48	30.57	18.95
	SOC	4.99	4.71	4.29	3.20	6	3.16
Atten.WM	LNS	11.04	8.68	17.29	8.28	15.71	5.96
	Stroop Test	28.05	20.48	27.29	16.57	25.14	8.15
Memory	HVLT	19.17	14.51	23	12.57	22.43	8.44
	Paragraph Recall	4.99	3.91	6.36	4.16	4.36	2.70
Language	BNT	9.57	6.63	11.71	5.28	13.29	1.80
	Similarities	13.89	9.94	20	9.15	21.57	3.10
VS	JLO	13.16	10.16	18.71	8.90	24.71	4.92
	HVOT	18.50	12.89	19.29	9.50	21	4.87
Global	MMSE	19.69	13.58	22.29	10.08	25.29	2.87
	PD-CRS	73.23	51.39	84.86	43.80	76.86	22.73
ADL	UPDRS-II	.71	.97	.66	.38	1.23	.72
QOL	PDQ-39	26.65	21.08	11.74	16.96	11.99	9.57
		Standard CT + tDCS		Tailored CT + tDCS		Control	
Domain	Outcome	*M*	*SD*	*M*	*SD*	*M*	*SD*
EF	COWAT	39.85	12.13	35.86	12.39	30.86	23.49
	SOC	9.14	2.27	8.57	2.37	4.43	4.39
Atten.WM	LNS	18.71	2.56	19.57	1.99	13.57	8.30
	Stroop Test	32.43	9.47	31	6.98	19.86	19.07
Memory	HVLT	31.14	4.22	25.43	6.21	19.57	11.53
	Paragraph Recall	6.64	1.95	6.43	2.41	2.93	1.64
Language	BNT	14	1	14.57	.53	10.29	4.92
	Similarities	21.57	1.90	21.71	4.27	17.86	8.03
VS	JLO	24	7.55	22.86	7.54	19.57	13.18
	HVOT	23.71	3.04	24.71	3.09	20.57	9.41
Global	MMSE	28.57	.98	26.71	1.80	21.57	10.11
	PD-CRS	97.86	16.75	91.57	12.25	68.43	39.26
ADL	UPDRS-II	.77	.35	1.16	.52	1.03	1.06
QOL	PDQ-39	12.80	11.83	12.76	12.80	15.45	16.28

Appendix H

Between group effect sizes based on change scores

					Comparison Group Effect Sizes (*g*)**				
H1	Group	Domain	Outcome	Time point*	Standard CT	Tailored CT	tDCS	Standard CT + tDCS	Tailored CT + tDCS
	Control	EF	COWAT	Post	.70	.42	.58	1.33	.70
				Follow-up	-.13	-.06	-.30	-.22	-.12
			SOC	Post	-1.19	-.51	-.13	**.41**	**.19**
				Follow-up	-.66	-.91	.14	**.23**	**.92**
		Atten./WM	LNS	Post	-.04	.19	.12	-.04	.02
				Follow-up	-.42	**.34**	.13	-.14	**.22**
			Stroop Test	Post	.35	.34	**.65**	**.60**	.14
				Follow-up	-.15	-.25	**.01**	**.24**	-.17
		Memory	HVLT	Post	.46	.05	.45	-.03	.37
				Follow-up	.51	.24	.03	.09	.22
			Para. Recall	Post	**.62**	.58	**1.11**	1.29	**1.36**
				Follow-up	1.30	.70	.28	.57	**1.75**
		Language	BNT	Post	-.55	.09	.30	.39	-.18

					Comparison Group Effect Sizes (*g*)**				
H1	Group	Domain	Outcome	Time point*	Standard CT	Tailored CT	tDCS	Standard CT + tDCS	Tailored CT + tDCS
	Control			Follow-up	.01	.69	.65	.77	.73
			Similarities	Post	.28	-.36	.13	**.59**	**1.06**
				Follow-up	-.98	-.55	-1.25	-.95	-1.58
		VS	JLO	Post	-.08	.49	.24	.37	.06
				Follow-up	**-.32**	.04	.18	-.23	-.28
			HVOT	Post	.06	.61	.24	.21	.54
				Follow-up	.33	.60	-.01	.05	.62
		GC	MMSE	Post	.41	.98	1.36	.46	.61
				Follow-up	.59	.35	.55	.50	.19
			PDCRS	Post	.44	.39	.53	.71	.51
				Follow-up	.27	.28	-.06	.10	-.02
		QOL	PDQ39	Post	**.24**	**.26**	.22	.27	-.14
				Follow-up	-.24	**.12**	.37	-.09	.27
		ADL	UPDRS-II	Post	**.33**	-.06	.32	**.55**	.34
				Follow-up	.28	.18	.24	.51	.22

					Comparison Group Effect Sizes (*g*)**				
H2	Group	Domain	Outcome	Time point*	Standard CT	Tailored CT	tDCS	Standard CT + tDCS	Tailored CT + tDCS
	Standard CT	EF	COWAT	Post	–	-.24	-.01	.34	-.11
				Follow-up	–	.05	-.20	-.09	.03
			SOC	Post	–	.76	1.21	1.71	1.40
				Follow-up	–	-.23	.79	.84	1.41
		Atten./WM	LNS	Post	–	.28	.17	.01	.09
				Follow-up	–	.86	.59	.40	.83
			Stroop Test	Post	–	.10	.45	.39	-.24
				Follow-up	–	-.22	.34	.66	-.05
		Memory	HVLT	Post	–	-.40	.02	-.62	-.23
				Follow-up	–	-.19	-.39	-.48	-.27
			Para. Recall	Post	–	.11	.40	.42	.54
				Follow-up	–	-.18	-.72	-.77	.50
		Language	BNT	Post	–	.83	.91	1.53	.53
				Follow-up	–	.87	.77	.99	1
			Similarities	Post	–	-.54	-.17	.12	.52

					Comparison Group Effect Sizes (*g*)**				
H2	Group	Domain	Outcome	Time point*	Standard CT	Tailored CT	tDCS	Standard CT + tDCS	Tailored CT + tDCS
	Standard CT			Follow-up	–	.52	-.45	-.16	-.96
		VS	JLO	Post	–	.65	.38	.55	.15
				Follow-up	–	.53	.65	.10	.03
			HVOT	Post	–	.58	.19	.16	.50
				Follow-up	–	.34	-.44	-.36	.35
		GC	MMSE	Post	–	.67	1.02	.00	.17
				Follow-up	–	-.40	-.04	-.24	-.54
			PDCRS	Post	–	.11	.23	.41	.14
				Follow-up	–	.08	-.37	-.18	-.50
		QOL	PDQ39	Post	–	-.02	-.04	.02	-.45
				Follow-up	–	.41	.67	.16	.53
		ADL	UPDRS-II	Post	–	-.55	-.03	.22	-.05
				Follow-up	–	-.20	-.08	.17	-.13

					Comparison Group Effect Sizes (*g*)**				
H3	Group	Domain	Outcome	Time point*	Standard CT	Tailored CT	tDCS	Standard CT + tDCS	Tailored CT + tDCS
	Tailored CT	EF	COWAT	Post	–	–	.20	.62	.17
				Follow-up	–	–	-.22	-.13	-.04
			SOC	Post	–	–	.44	1.02	.72
				Follow-up	–	–	1.04	1.08	1.64
		Atten./WM	LNS	Post	–	–	-.04	-.38	-.31
				Follow-up	–	–	-.23	-.66	-.24
			Stroop Test	Post	–	–	.25	.22	-.25
				Follow-up	–	–	.52	.78	.17
		Memory	HVLT	Post	–	–	.39	-.08	.29
				Follow-up	–	–	-.19	-.17	-.04
			Para. Recall	Post	–	–	.19	.17	.27
				Follow-up	–	–	-.40	-.35	.55
		Language	BNT	Post	–	–	.25	.38	-.35
				Follow-up	–	–	.05	.06	-.07
			Similarities	Post	–	–	.44	.95	1.37

					Comparison Group Effect Sizes (*g*)**				
H3	Group	Domain	Outcome	Time point*	Standard CT	Tailored CT	tDCS	Standard CT + tDCS	Tailored CT + tDCS
	Tailored CT			Follow-up	–	–	-.88	-.54	-1.30
		VS	JLO	Post	–	–	-.28	-.20	-.41
				Follow-up	–	–	.21	-.37	-.42
			HVOT	Post	–	–	-.39	-.42	-.08
				Follow-up	–	–	-.80	-.71	.01
		GC	MMSE	Post	–	–	.12	-.73	-.59
				Follow-up	–	–	.35	.25	-.24
			PDCRS	Post	–	–	.07	.16	-.02
				Follow-up	–	–	-.36	-.21	-.40
		QOL	PDQ39	Post	–	–	-.03	.06	-.56
				Follow-up	–	–	.30	-.24	.18
		ADL	UPDRS-II	Post	–	–	.57	1	.68
				Follow-up	–	–	.13	.80	.09

					Comparison Group Effect Sizes (*g*)**				
H4	Group	Domain	Outcome	Time point*	Standard CT	Tailored CT	tDCS	Standard CT + tDCS	Tailored CT + tDCS
	tDCS	EF	COWAT	Post	–	–	–	.27	-.08
				Follow-up	–	–	–	.14	.25
			SOC	Post	–	–	–	.66	.36
				Follow-up	–	–	–	.10	.81
		Atten./WM	LNS	Post	–	–	–	-.19	-.13
				Follow-up	–	–	–	-.33	.07
			Stroop Test	Post	–	–	–	-.03	-.59
				Follow-up	–	–	–	.42	-.38
		Memory	HVLT	Post	–	–	–	-.59	-.23
				Follow-up	–	–	–	.05	.17
			Para. Recall	Post	–	–	–	-.04	.11
				Follow-up	–	–	–	.13	1.13
		Language	BNT	Post	–	–	–	.00	-.54
				Follow-up	–	–	–	-.01	-.11
			Similarities	Post	–	–	–	.38	.83

					Comparison Group Effect Sizes (*g*)**				
H4	Group	Domain	Outcome	Time point*	Standard CT	Tailored CT	tDCS	Standard CT + tDCS	Tailored CT + tDCS
	tDCS			Follow-up	–	–	–	.20	-.55
		VS	JLO	Post	–	–	–	.12	-.17
				Follow-up	–	–	–	-.50	-.55
			HVOT	Post	–	–	–	-.04	.31
				Follow-up	–	–	–	.08	.82
		GC	MMSE	Post	–	–	–	-1.18	-.97
				Follow-up	–	–	–	-.19	-.50
			PDCRS	Post	–	–	–	.08	-.12
				Follow-up	–	–	–	.17	.07
		QOL	PDQ39	Post	–	–	–	.07	-.45
				Follow-up	–	–	–	-.52	-.09
		ADL	UPDRS-II	Post	–	–	–	.27	-.02
				Follow-up	–	–	–	.34	-.05

					Comparison Group Effect Sizes (*g*)**				
H5	Group	Domain	Outcome	Time point*	Standard CT	Tailored CT	tDCS	Standard CT + tDCS	Tailored CT + tDCS
	Standard CT + tDCS	EF	COWAT	Post	–	–	–	–	-.58
				Follow-up	–	–	–	–	.14
			SOC	Post	–	–	–	–	-.22
				Follow-up	–	–	–	–	.69
		Atten./WM	LNS	Post	–	–	–	–	.12
				Follow-up	–	–	–	–	.65
			Stroop Test	Post	–	–	–	–	-.53
				Follow-up	–	–	–	–	-.68
		Memory	HVLT	Post	–	–	–	–	.67
				Follow-up	–	–	–	–	.15
			Para. Recall	Post	–	–	–	–	.18
				Follow-up	–	–	–	–	1.26
		Language	BNT	Post	–	–	–	–	-.89
				Follow-up	–	–	–	–	-.18
			Similarities	Post	–	–	–	–	.57

					Comparison Group Effect Sizes (*g*)**				
H5	Group	Domain	Outcome	Time point*	Standard CT	Tailored CT	tDCS	Standard CT + tDCS	Tailored CT + tDCS
	Standard CT + tDCS			Follow-up	–	–	–	–	-.65
		VS	JLO	Post	–	–	–	–	-.28
				Follow-up	–	–	–	–	-.06
			HVOT	Post	–	–	–	–	.34
				Follow-up	–	–	–	–	.73
		GC	MMSE	Post	–	–	–	–	.20
				Follow-up	–	–	–	–	-.46
			PDCRS	Post	–	–	–	–	-.26
				Follow-up	–	–	–	–	-.16
		QOL	PDQ39	Post	–	–	–	–	-.54
				Follow-up	–	–	–	–	.39
		ADL	UPDRS-II	Post	–	–	–	–	-.33
				Follow-up	–	–	–	–	-.51

Note. Bolded effect sizes correspond with results reported in text. *H* = hypothesis; *g* = Hedge's *g*; CT = cognitive training; tDCS = transcranial direct current stimulation; * = post changes scores calculated using 'pre-intervention mean – post-intervention mean' and follow-up change scores calculated using 'pre-intervention mean – follow-up intervention mean'; ** = positive effect sizes favour comparison group.