Associations Between EEG and Cognition in Parkinson's Disease

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Abstract

Parkinson's disease (PD) is a progressive neurodegenerative disorder that is accompanied by a range of both motor and non-motor symptoms. Cognitive impairment in PD is particularly common, with a high incidence of conversion to dementia (PDD). Electroencephalogram (EEG) brain activity may provide a cost-effective and relatively quick technique to determine neural correlates of cognitive status in PD. We used EEG to measure spontaneous brain activity during eyes-closed resting wakefulness and evoked response potentials (ERPs) during a three-stimulus visual oddball task.

The oddball task was initially used to compare easy and hard options in a group of 19 cognitively 'normal' PD participants (PD-N) compared to 19 healthy controls (HC). PD-N status was established by not meeting Movement Disorder Society Task Force (MDS-TF) level II criteria for PD with mild cognitive impairment (PD-MCI). Overall, reaction time was longer for the hard task, and longer in the PD-N group than the HC group, but no group differences were found for amplitude or latency, for either the P3a or P3b ERPs. The easy oddball task was then used to compare participants in four groups: 23 HC, 31 PD-N, 26 PD-MCI, and 8 PDD. New Zealand Brain Research Institute PD-MCI criteria were used that are consistent with the MDS-TF Level II criteria, but specifically based on two tests in each of five cognitive tests that predict a high risk of conversion to PDD once impairment is evident on any two tests. The median reaction time was longer in the PD-N group compared to the HC group, longer again for the PD-MCI group, and longest in the PDD group. However, no significant differences among any groups were found for ERP amplitude or latency, for either the P3a or P3b.

Individual alpha frequency (IAF), spectral power (delta, theta, alpha, and beta) and debiased weighted phase lag index (dwPLI) functional connectivity (for each band) were derived from 10-minutes of resting-state EEG in 29 HC, 44 PD-N, 40 PD-MCI, and 12 PDD participants. Group differences were evident for the peak alpha frequency (Individual Alpha Frequency; IAF) between all groups except between the HC and PD-N groups. IAF was lower in the PD-MCI group and decreased further in the PDD group. Spectral power was highest in the theta band and lowest in the alpha band for the PDD

group. Group differences in alpha power were evident in the posterior brain region, smaller in the central region, but not evident the anterior brain region. For the posterior region, alpha power was highest in the HC group and decreased linearly across PD-N, PD-MCI and PDD groups. Spectral power in the theta band was intermediate in the PD-MCI group compared to the PDD group and the PD-N and HC groups; the latter two groups had similar theta power.

Across groups, functional connectivity was also highest in the alpha band, and lowest in the theta band, for the PDD group. This was apparent for both the within-region and cross-region connectivity analyses. For the theta band, the PD-MCI group had intermediate functional connectivity values, for both types of region analysis. For the alpha band, the PD-MCI group showed intermediate values for the within-region analysis but was similar to the PD-N and HC groups for the cross-region analysis.

Overall, resting-state measures proved to be good discriminators of cognitive status on EEG, unlike oddball ERP measures. For resting-state, spectral power measures produced clearer group differences for PD-MCI and PDD than functional connectivity measures. Spectral power in the alpha band, especially in the posterior region, showed the largest effect sizes for between-group comparisons. Longitudinal work is needed to establish whether EEG measures are good predictors of future cognitive decline in PD.

In this project, we were the first to look at task difficulty in a sample of cognitively unimpaired PD patients who did not meet criteria for PD-MCI. Overall task difficulty did not produce any significant ERP differences between tasks or groups. We then used the ‘easy’ task to investigate group differences in HC, PD-N, PD-MCI, and PDD groups, but no significant group differences were found for either P3a or P3b. For resting-state, we were the first to look at IAF across the four groups, namely HC, PD-N, PD-MCI, and PDD. IAF decreased linearly from the HC group to the PDD group in the posterior brain region. We were also the first to use dwPLI to calculate functional connectivity in the resting-state. We have shown that alpha band functional connectivity was lowest, and theta band functional connectivity highest in the PDD group; the other three groups tended to be similar, with only weak evidence that the PD-MCI group showed intermediate values for connectivity.

These studies provided a promising endeavour into resting-state and task-related EEG measures across the full spectrum of cognition. The findings have implications of developing markers for future cognitive decline in PD.

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Preface

This thesis is submitted for the degree of Doctor of Philosophy at the University of Canterbury, Christchurch, New Zealand. The research was conducted under the primary supervision of Professor John Dalrymple-Alford of the School of Psychology, Speech and Hearing, University of Canterbury. The thesis was co-supervised by Professor Richard Jones of the Department of Electrical Engineering, University of Canterbury, Dr Reza Shoorangiz of the New Zealand Brain Research Institute, Christchurch, Professor Tim Anderson of the Department of Medicine, University of Otago, Christchurch, Associate Professor Roeline Kuijer of the School of the Psychology, Speech and Hearing, University of Canterbury and Professor Ian Kirk of the School of Psychology, University of Auckland, Auckland.

The data that has been used in combination with electroencephalogram (EEG) data collected by myself, for this thesis are part of the New Zealand Brain Research Institute's longitudinal Parkinson's disease (PD) cohort which has been collected from the Parkinson's patients who live in Canterbury, New Zealand over the past 13 years. Over this period 163 PD patients and 48 healthy control participants have been assessed. My contribution to this data set has been through the collection of EEG and neuropsychological data and the quality control with the storage of this data. I have conducted over 145 EEG sessions and over 130 corresponding neuropsychological assessments of PD patients and healthy older adults living in Christchurch, scored over 130 assessments and checked that the data was scored and entered correctly into the database made specifically for this study. Some participants returned for a follow up session and these people only had one session included in the data. The remaining data was conducted by Research Assistants employed at the New Zealand Brain Research Institute. I would like to especially acknowledge and thank Dr Reza Shoorangiz for his part in pre-processing all the EEG data for me to complete the analysis. I would like to thank everyone who has contributed to the data collection over the course of this thesis, but in particular Katy Jones, who was employed as a part time Assistant Research Fellow to conduct EEG and neuropsychological sessions, and as part of her contribution, scored and entered the neuropsychological data into a database. I would also like to thank Leslie Livingston and Marie Goulden, the study co-ordinators, for all their hard

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Publications

Abstracts

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Peterson, E., Shoorangiz, R., Livingstone, M., Elias, B., Jones, R.D., Tippett, L., Anderson, T.J., Kirk, I. J., Dalrymple-Alford, J.C. (2018). Oddball event-related potentials in Parkinson's disease patients with normal cognition. *A Proceedings of the International Australasian Winter Conference on Brain Research (AWCBR),* Queenstown, New Zealand, 35, Abstract 9.17

Shoorangiz, R., **Peterson, E.,** Elias, B., Livingstone, M., Jones, R.D., Tippett, L., Anderson, T.J., Kirk, I.J., Dalrymple-Alford, J.C. (2018). EEG-based resting-state functional connectivity in Parkinson's disease with normal cognition. *A Proceedings of the International Australasian Winter Conference on Brain Research (AWCBR*), Queenstown, New Zealand, 36, Abstract 9.39

Peterson, E., Shoorangiz, R., Jones, R., Livingston, L., Kirk, I., Tippett, L., Livingstone, M., Kuijer, R., Anderson, T., Elias, B., Dalrymple-Alford, J. (2019). Task difficulty and the three-stimulus oddball task in patients with PD. *A Proceedings of the International Congress of Parkinson's Disease and Movement Disorders (MDS),* Nice, France, 23, Abstract 1719.

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Abbreviations

AD	Alzheimer's disease
ADAS-Cog	Alzheimer's disease Assessment Scale - Cognitive
ADD	Alzheimer's disease with Dementia
ADL	Activities of Daily Living
AD-MCI	Alzheimer's disease with Mild Cognitive Impairment
ANOVA	Analysis of Variance
AZSAND	Arizona Study of Aging and Neurodegenerative Disorders
BVMT	Brief Visuospatial Memory Test
CDR	Clinical Dementia Rating Scale
CERAD	Consortium to Establish a Registry for Alzheimer's disease
CI	Confidence Interval
CVLT	California Verbal Learning Test
DLB	Dementia with Lewy Bodies
DRS	Dementia Rating Scale
DSM	Diagnostic and Statistical Manual for Mental Disorders
dwPLI	Debiased Weighted Phase Lag Index
EEG	Electroencephalogram
EMG	Electromyographic
EOG	Electrooculography

ERP	Event related potential
fMRI	functional magnetic resonance imaging
HADS	Hospital Anxiety and Depression Scale
HC	Healthy control
HZ	Hertz
GDS	Geriatric Depression Scale
IAF	Individual Alpha Frequency
IN	Intellectually normal
ISI	Interstimulus intervals
LEDD	Levodopa Equivalent Daily Dose
LLC	Lagged Linear Connectivity
LOO	Leave-one-out
MCI	Mild Cognitive Impairment
MEG	Magnetoencephalography
MDS	Movement Disorders Society
MDS-TF	Movement Disorders Society Task Force
min	Minute
MMN	Mismatched Negativity
MMSE	Mini-Mental State Examination
MoCA	Montreal Cognitive Assessment

ms	Milliseconds
NA	Not available
NZBRI	New Zealand Brain Research Institute
OA	Older Adults
PET	Positron Emission Tomography
PD	Parkinson's disease
PD-MCI	Parkinson's disease with mild cognitive impairment
PDD	Parkinson's disease with Dementia
PD-N	Non-demented Parkinson's disease
PLI	Phase Lag Index
QEEG	Quantitative Electroencephalogram
RT	Reaction time
s	Seconds
SD	Standard Deviation
SDMT	Symbol Digit Modalities Test
SE	Standard Error
TF	Transition Frequency
UK	United Kingdom
UKPDSBB	United Kingdom Parkinson's Disease Society Brain Bank
UPDRS	Unified Parkinson's Disease Rating Scale

WPLI	Weighted Phase Lag Index
WTAR	Wechsler Test of Adult Reading
YA	Younger Adults
VOSP	Visual Object and Space Perception Batt

Chapter 1: Introduction

1.1 Overview

Parkinson's disease (PD) is a progressive neurodegenerative disease that is primarily a consequence of degeneration of the substantia nigra pars compacta and requires long-term medication and treatment for the remainder of the patient's life (Chaudhuri, Healy, & Schapira, 2006). PD also increases caregiver burden, has a major impact on well-being, and significantly effects quality of life (Fang, Lv, Mao, Dong, & Liu, 2020; Hindle, Petrelli, Clare, & Kalbe, 2013; Lawson et al., 2016). PD affects 2-3% of the older New Zealand population, with rates projected to double by 2040 (Myall et al., 2017). PD is now well accepted to be more than just a motor disorder, with non-motor symptoms having a significant impact on an individual's functioning and wellbeing (Hindle et al., 2013; Lawson et al., 2016). Cognitive impairment and progression to dementia are among these non-motor symptoms, with many individual's progressing to dementia over their disease duration (Aarsland et al., 2017; Roheger, Kalbe, & Liepelt-Scarfone, 2018). This progression can vary anywhere from 2-25 years after diagnosis and is a significant part of the disease process. The changes in brain function associated with cognitive decline and progression to dementia are not well understood, which makes determining the efficacy of interventions and potential treatments extremely difficult. Therefore, using the electroencephalogram (EEG) could identify some of those changes and provide a better understanding of the disease progression.

1.2 Motivation

EEG is a feasible, low-cost, and non-invasive method which can be used to investigate various aspects of the brain function, such as spectral power, individual alpha frequency (IAF), functional connectivity, and event-related potentials in PD (Al-Qazzaz et al., 2014; Bridwell et al., 2018). EEG data can be collected multiple times over the disease duration and poses no risk to the individual being assessed. EEG recordings can be extremely helpful to determine how different areas of the brain communicate with each other. Analysing brain activity may lead to biomarkers that can help to (1) estimate a participant's cognitive ability and (2) determine the risk of progression to dementia (PDD) in the future.

Mild cognitive impairment in PD (PD-MCI) is a prodromal state for PDD and is used to identify those whose cognition ability is less than expected for their age (Weil, Costantini, & Schrag, 2018). Previous literature has suggested MCI to be the strongest predictor for PDD (Hoogland et al., 2017; Hoogland, Post, & de Bie, 2019). There are several common criteria used in the literature to characterise cognition in PD, but the current classification is to primarily identify anyone who meets MDS Task Force Level I criteria which requires a participant to have at least two impairments in any 10 neuropsychological tests at -1.5 SD, relative to normative tables. These participants would be identified as "PD-MCI, at elevated risk of PDD within 3.5-4.5 years". Participants would be classified as PDD if they had two impairments at -2 SD in any domain as well as evidence of significant decline from daily activities not attributed to motor impairments. The five core domains include: executive function, attention, working memory and speed of processing, episodic memory, visuoperceptual, and language. Myall et al. (2020) extended prior PD-MCI work and identified ten neuropsychological measures that are particularly relevant for progression to PDD within 4 years from the neuropsychological assessments. This criterion consists of ten sensitive neuropsychological measures across the five cognitive domains, developed at the New Zealand Brain Research Institute (NZBRI), and was used in this thesis to characterise each participant's cognitive status at the time of their EEG session.

1.3 Objectives

The thesis aims to determine EEG markers of cognitive ability in PD, by investigating resting state measures as well as a three-stimulus visual oddball task. Identification of PD-MCI will be based on Myall et al. (2020) criteria from the NZBRI, that focus on 10 sensitive tests over five domains. Finally, a subset of participants in the study completed two versions of the visual oddball task which allowed us to look at the difference between ERPs and tasks to determine any task difficulty effects. The implications of this project are to use these EEG markers of cognitive ability in PD to identify those at a heightened risk of progression to dementia. Early identification of these participants would be beneficial for various therapeutic interventions such as cognitive training and brain stimulation techniques, as well as medications to slow down disease progression and improve participants overall quality of life.

1.4 Thesis Organisation

This thesis begins by discussing the PD literature with a focus on the non-motor symptoms, in particular cognitive decline *(Chapter 2)* and then discusses the prior EEG literature in PD with a focus on the resting state task and the oddball paradigm, and outlines the study aims and objectives *(Chapter 3).* The findings of the four research chapters are discussed in the following chapters *(Chapter 4-7)*. The research chapters assess (1) the effect of task difficulty between patients with PD who are characterized as cognitively "normal", and compares these patients with healthy controls (HC) *(Chapter 4),* (2) the use of a three-stimulus visual oddball to investigate ERPs, in a spectrum of PD patients *(Chapter 5),* (3) the resting state using spectral power and individual alpha frequency (IAF) measures in a spectrum of cognition in PD *(Chapter 6),* and (4) the use of functional connectivity in a spectrum of cognition in PD to evaluate the resting state task *(Chapter 7).* This thesis looks at differences between groups that have previously been characterized using the criteria outlined by Myall et al. (2020). Finally, the overall findings are discussed along with a critique of the study and future directions *(Chapter 8).*

Chapter 2: Cognition in Parkinson's disease

2.1 Overview of Parkinson's disease

Parkinson's disease (PD) is a progressive neurodegenerative disorder. It was named after James Parkinson who first described the motor condition during the 19th century when it was known as "shaking palsy" (Jankovic, 2008). The cardinal motor symptoms of PD include bradykinesia, rigidity, rest tremor and loss of postural reflexes (Jankovic, 2008). This condition is, however, also accompanied by a wide range of non-motor symptoms. These non-motor symptoms have significant implications for everyday functioning, personal care, caregiver burden, and health-related costs (Antonini et al., 2012; Chaudhuri & Schapira, 2009). The key motor impairments are primarily caused by depleting levels of dopamine in the striatum as a consequence of degeneration of the substantia nigra pars compacta (Chaudhuri et al., 2006). In fact, the appearance of the motor-symptoms may be a "midpoint" in the disease process for many patients, before motor and non-motor symptoms worsen after the explicit clinical diagnosis (Hawkes, Del Tredici, & Braak, 2010). Medication, such as levodopa, is often prescribed to manage some of the motor symptoms, especially for the key problem of bradykinesia. There is, however, no current cure for Parkinson's disease. Therefore, managing the symptoms becomes foremost in order to sustain a healthy well-being in these patients (Politis et al., 2010).

Although PD can occur in adults at any age, most cases are seen in those over 60 years of age. The progression differs across individuals in terms of severity and complexity (Postuma et al., 2015). The disease duration is generally associated with symptom severity and frequency. Although motor impairments worsen over time, there are also increasingly worsening autonomic, psychiatric, and especially cognitive symptoms in most patients. A major concern is the high frequency of severe cognitive impairments that lead to Parkinson's disease with dementia (PDD) (Aarsland et al., 2017; Nijkrake et al., 2007). There are several theories surrounding cognition in PD and progression to PDD, although no definitive processes have been identified for cognitive decline (Gratwicke, Jahanshahi, & Foltynie, 2015).

2.2 Dual-syndrome hypothesis in Parkinson's disease

A recent theory surrounding the cognitive deficits in PD and progression to PDD is the dual syndrome hypothesis (Kehagia, Barker, & Robbins, 2013). This theory suggests that posterior cortical function, underpinned by declining cholinergic projections, especially to temporal and posterior cortical brain regions, is associated with cognitive impairment related to progression to PDD (Kehagia et al., 2013). In contrast, frontally mediated changes are considered more related to dopamine dysfunction that may be unrelated to progression to PDD (Kehagia et al., 2013). Bohnen et al. (2006) suggests that cholinergic hypofunction may also influence frontal processing efficiency, and this could still be related to progression.

The dual-syndrome hypothesis is a complex hypothesis which encompasses the original theory of the degeneration of dopaminergic neurons in the brain for those with PD (Kehagia et al., 2013). Recent literature suggests that the executive deficits in PD may not be limited to the fronto-striatal network alone and that other networks may be involved in this degeneration in patients with the disease (Gratwicke et al., 2015). Due to this suggestion, the dual-syndrome hypothesis is of interest to this study as we will use electroencephalogram (EEG) metrics across broad frontal, central and posterior electrode regions in PD patients. By investigating these regions, our study aims to determine whether EEG can be used to examine the association between regional changes and cognitive decline in PD, especially in patients classified as PD-MCI and PDD. Although cognitive decline is the focus of this thesis, it is worth acknowledging the motor and other non-motor symptoms that also have a significant effect on a patient's well-being and their quality of life in PD (Hindle et al., 2013; Lawson et al., 2016). The most prevalent motor and non-motor symptoms are outlined below.

2.3 Motor Symptoms in Parkinson's disease

Bradykinesia is defined as "slowness of movement and decrement in amplitude or speed (or progressive hesitations/halts) as movements are continued" (Postuma et al., 2015). Initially, this will occur unevenly across left and right limbs. Treatment for bradykinesia can generally be managed by taking levodopa. Although initially effective, after

approximately 5 years it can have a “wearing off” effect and dyskinesia may emerge (Griffiths et al., 2012).

Rigidity is identified as passive resistance to movement of major joints when the patient is in a relaxed position and the examiner manipulates the limbs and neck (Postuma et al., 2015). This is caused by stiffness in muscles and often impairs voluntary movements. Muscle stiffness can lead to rigidity in the joints and, alongside bradykinesia, is often evaluated using the Unified Parkinson’s Disease Rating Scale (UPDRS) (Prochazka et al., 1997).

Rest tremor is also more frequently recognised as unilateral, but generally should disappear when the individual begins a task or during sleep (Jankovic, 2008). Importantly, this rest tremor must be defined when the limb is at full rest. It generally has a frequency of between 4 and 6 Hz and is suppressed during the initiation of movement of the limbs but may reappear, or “re-emerge”, as the movement slows down or stops (Postuma et al., 2015).

2.4 Non-motor Symptoms in Parkinson’s disease

Given the impact of motor symptoms on patients, it is salient that non-motor symptoms often cause greater distress for the patient, have more impact on caregivers and whanau, and increase mortality (Antonini et al., 2012; Backstrom et al., 2018; Jones et al., 2017; Tibar et al., 2018). Non-motor symptoms in PD, especially cognitive impairment, have become increasingly recognised during the past decade (J. Goldman et al., 2018; Weintraub, Troster, Marras, & Stebbins, 2018). It is important to recognise that the presence and severity of non-motor symptoms need not correspond with the severity of motor impairment (Chaudhuri & Schapira, 2009). Jankovic (2008) described common symptoms to include cognitive impairment, depression, anxiety, apathy, and hallucinations. Impulsive behaviours are among other commonly reported symptoms and include binge eating, compulsive shopping, gambling, and obsessive-compulsive behaviour such as consistently rearranging objects and sorting items. Impulsive behaviour is associated with the dysregulation of dopamine due to dopaminergic medications, but the mechanism for this dysregulation is unclear (Weintraub et al., 2006). Other common symptoms of PD include soft voice, micrographia, impaired sense of smell, urinary

urgency, excessive sweating, sexual dysfunction, depression, fatigue, pain, sleep disturbance, autonomic dysfunction.

Cognitive decline in PD is of particular relevance to this thesis. Cognitive symptoms have a significant impact on morbidity and well-being (Backstrom et al., 2018; Fang et al., 2020). The evolution of cognitive symptoms has become central to understanding the broader clinical problems experienced by people with PD and their suitability for relevant treatment strategies at different points in the disease course (Aarsland et al., 2017). Particularly poignant is the high incidence of conversion to dementia (PDD), which occurs in about 50% within 10 years of diagnosis and up to 80% of all cases (Lawrence, Gasson, & Loftus, 2016). The prevalence of PDD is about 30-40% (Nicoletti et al., 2019). Another study reported that the prevalence of PDD may be about six-fold for age-matched people who do not have a neurological condition (Chaudhuri et al., 2006; Emre, 2003). The prevalence of PDD in those with PD has been shown to have a significant impact on individuals in a study which reported that cognitive decline had the greatest impact on quality of life in their patients (Lawson et al., 2016).

2.4.1 Medication effects on cognition in Parkinson's Disease

Medications are an effective way of treating and alleviating the symptoms of PD in many patients. There are various medications available for treating the motor and non-motor symptoms of PD. The most common medication prescribed for motor symptom management is the dopamine precursor, levodopa. This medication has proven to be effective in relieving rest tremor and bradykinesia (Tambasco, Romoli, & Calabresi, 2018). Although this medication is widely used and effectively tolerated, long-term use has shown an increased risk of developing dyskinesia (Whitney, 2007). Dopamine receptor agonists e.g. ropinirole and pergolide, are also commonly prescribed and have been shown to be beneficial in relieving motor symptoms. Common side effects of dopamine receptor agonists include obsessive compulsive behaviours as well as nausea, dizziness, fatigue and hallucinations (Whitney, 2007).

Although medications have shown beneficial evidence in relieving motor symptoms in PD, few studies have investigated the relationship between medication and the effect on non-motor symptoms, specifically cognition. One study investigated the effects dopamine has on cognitive functioning and working memory in PD (Costa, Peppe,

Dell'Agnello, Caltagirone, & Carlesimo, 2009). It reported that after administration of a dopamine receptor agonist, working memory accuracy was improved in PD patients who had been classified as being in the low-performer group. In the high-performance group, there was no effect of the drug (Costa et al., 2009). Another study investigated the relationship between dopamine receptor agonists and cognitive function in mild PD (Brusa et al., 2005). Patients were given baseline and follow-up assessments after an 8-week trial of taking either the dopamine receptor agonist or a dopamine precursor. Results determined no significant difference between assessment scores, and therefore concluded that the dopamine receptor agonist neither improved nor impaired cognitive function in their patient group (Brusa et al., 2005).

A recent review summarised the effects medication can have on cognition in PD (Kehagia et al., 2013). They reported that several studies suggest medication impairs cognition, whereas other studies reported no impairment (Cools, Stefanova, Barker, Robbins, & Owen, 2002; Owen, Sahakian, Summers, Hodges, & Polkey, 1995). One study suggested there were beneficial effects of dopaminergic medication on working memory, but no effects on visual recognition (Owen et al., 1995). They also suggested that the cognitive effects found in PD are due to the dopamine loss and the dopaminergic medication may provide a restorative effect of cognitive functioning. Another study reported that dopaminergic medication can impair visual and spatial memory in PD (Sahakian et al., 1988).

Donepezil is in another class of medications called cholinesterase inhibitors and has previously been used for patients with PD (Aarsland, Laake, Larsen, & Janvin, 2002; Ravina et al., 2005). Previous literature has looked at the efficacy of this medication for the treatment of cognition in patients who had PDD (Ravina et al., 2005). Treatment periods were 10 weeks and patients were monitored closely throughout this period. Donepezil was reported to be well tolerated and the adverse effects of the medication on cognition were mild and did not worsen PDD. Due to conflicting results in the literature surrounding the effect of medication on cognition in PD, considering these effects in future research would be beneficial.

2.5 Cognition in Parkinson's disease

While cognitive decline generally increases in PD patients, the rate of decline is substantially heterogeneous (Greenland, Williams-Gray, & Barker, 2019). A better understanding of factors associated with conversion and non-conversion is therefore needed. One method of capturing some of this heterogeneity is to identify patients who have "mild cognitive impairment" (MCI) which is a relatively recent concept specifically in the context of PD (Litvan et al., 2012). The term MCI, introduced in the late 1980s, is used to identify those whose cognitive ability is less than expected for their age, (Weil et al., 2018), or their expected premorbid levels (Marras et al., 2013). PD-MCI is of course, a prodromal state for PDD (J. Goldman & Litvan, 2011). However, debate continues as to whether all cognitive impairments are harbingers for PDD (Barker & Williams-Gray, 2014; Gratwicke et al., 2015), although clear evidence from large multinational studies, which includes data from the NZ Brain Research Institute, confirm that a PD-MCI status is probably the strongest predictor for PDD (Hoogland et al., 2017; Hoogland et al., 2019). About 50% of PD-MCI patients progress to PDD over a 4-year period (Wood et al., 2016).

There can, however, be many reasons why participants may be classified as PD-MCI, including medications, depression, infection, metabolic disturbance or low baseline cognitive function due to low educational attainment (Barker & Williams-Gray, 2014). MCI may be present in the form of frontal-lobe damage in up to 50% of PD patients (Kehagia et al., 2013). Due to the complexity of PD-MCI classification, the recent Movement Disorder Society Task Force (MDS-TF) criteria attempted to exclude participants who have poor cognitive performance due to co-morbid conditions or severe affective or psychiatric disturbance, that would otherwise have been classified as PD-MCI (Barker & Williams-Gray, 2014).

There are several common criteria used in the literature to characterise PD and PD-MCI. These criteria use various neuropsychological tests combined with clinical measures to determine a patient's cognitive status and whether the cognitive impairment present meets their criteria for PD-MCI. The most common criteria used in the PD literature are the MDS-PD for PD-MCI.

2.6 Criteria for defining Parkinson's disease

Postuma et al. (2015) have reported the most recent MDS-TF criteria which have been adapted and updated from Litvan et al. (2012). These updated criteria define PD in terms of the three cardinal motor features: bradykinesia, rigidity and rest tremor. Bradykinesia, especially when present with fatiguing (decline in movement speed/amplitude over time) is the main symptom that needs to be present for a diagnosis, in combination with either rest tremor, rigidity, or both (Postuma et al., 2015). The MDS-PD criteria have a three-step process in which step one defines Parkinsonism in terms of the three cardinal motor features, and if these criteria are not met then step two considers prodromal PD or non-clinical PD. The third step looks at any red flags that may be present such as rapid progression of gait impairment, an absence of motor symptoms over a 5-year period not related to treatment, or severe autonomic dysfunction (Marsili, Rizzo, & Colosimo, 2018). If more than two red flags are present, clinical PD cannot be diagnosed (Marsili et al., 2018).

The UKPDSBB diagnosis criteria are similar to the MDS-PD criteria and use a three-step process as well. Step one outlines that bradykinesia must be present with at least one of the following: muscular rigidity, 4-6 Hz rest tremor, and postural instability not caused by primary visual, vestibular, cerebellar, or proprioceptive dysfunction (Marsili et al., 2018). Step two outlines the exclusion criteria and step three is supported positive criteria for PD where three or more symptoms are required for a definite PD diagnosis in combination with step one. These symptoms are unilateral, rest tremor present, progressive disorder, persistent asymmetry affecting side of onset most, excellent response to levodopa, severe levodopa-induced chorea, levodopa response for 5 or more years and clinical course of ten years or more.

2.7 Criteria for characterising PD-MCI in Parkinson's disease

There are changing perspectives on conversion to PDD in the recent literature. This is due to the different methods for characterising PD-MCI as well as the processes affected in the brain to progress to PD-MCI and then eventually to PDD. Hoogland et al. (2017) investigated mild cognitive impairment as a risk factor for PDD to determine the validity of the current MDS criteria for PD dementia. Four studies were included in

their analysis to look at the predictive value of the level II criteria and longitudinal follow-up for conversion to dementia. They concluded that there was a trend of increasing hazard of PDD with declining neuropsychological performance. They also reported that participants progress to PDD at a much higher rate if they have PD-MCI, but this progression is not always inevitable due to the limitation of not being able to predict a direct generalisation of the results to the individual patient level (Hoogland et al., 2017). This suggests that there may be some variability in the direct progression to PDD according to their findings and limitations.

A recent paper outlined ten cognitive tests able to identify high risk of conversion to dementia in PD (Myall et al., 2020). This paper followed and extends prior PD-MCI work (Wood et al., 2016). The key difference between prior work and that of Myall et al. (2020) is the identification of neuropsychological measures which are particularly relevant for progression to PDD. These measures are the first to determine which specific neuropsychological impairments convey the highest risk of conversion to PDD (Myall et al., 2020). Identifying a patient's risk of progression to PDD would help to identify prognosis and specific care and management plans for the patient. Patients included in this study were followed for four years after completing a baseline assessment. Twenty-one measures taken from 16 neuropsychological tests over 5 cognitive domains were used to investigate the value of each test as a predictor for conversion to PDD. The prediction value for conversion to PDD when a patient was identified as cognitively impaired improved by 51% when 10 test measures were selected. Therefore, the authors concluded that the abbreviated selection of ten neuropsychological tests can identify patients that are at high risk of conversion to PDD over the following four years. They also reported that these abbreviated tests would be extremely beneficial when extensive neuropsychological testing is not feasible (Myall et al., 2020).

As outlined above, there are various criteria for characterising cognition in PD which are commonly used across the literature (Litvan et al., 2012; Marsili et al., 2018; Postuma et al., 2015; Wood et al., 2016). The addition of ten cognitive tests that are able to mainly identify high risk of conversion to PDD (Myall et al., 2020), has provided a new measurement tool to characterise cognition in PD using an abbreviated selection of neuropsychological tests. The basis of this thesis is set around using the ten tests

mentioned above from Myall et al. (2020) to classify cognition in our population of PD patients at the NZBRI.

2.7.1 Clinical overlap of PD-MCI and AD-MCI

Alzheimer's disease (AD) and PD are not normal ageing; however, ageing may play a part in terms of additional pathology that puts people at greater risk of dementia (Fjell et al., 2014). AD and (AD-)MCI diagnostics are driven on the basis that memory impairment is paramount, especially when the full set of neuropathology biomarkers are not available (Frisoni et al., 2017; Karantzoulis & Galvin, 2011).

PD-MCI requires a primary diagnosis for PD first, which is determined by an experienced movement disorder neurologist and specific criteria for PD (Jankovic, 2008; Postuma et al., 2015). Although it has been suggested that Alzheimer neuropathology be a critical factor for cognitive decline in PD, evidence from the NZBRI (Melzer et al., 2019) shows that increased amyloid on PET scanning does not clearly differentiate cognitively impaired from other PD. The relative contribution of tau neuropathology is not known, but the dominant factor is probably the spread of alpha-synuclein neuropathology (Braak & Del Tredici, 2017).

Moreover, in PD, impairments from all cognitive domains are treated equally; there is no explicit focus on any domain. In PD, two impairments are required (Litvan et al., 2012). Overall, there are differences between AD and PD, with broader criteria used for PDD than has been used in the past for AD (Litvan et al., 2012; Myall et al., 2020; Wood et al., 2016).

2.8 Summary

Parkinson's disease is a complex, debilitating neurodegenerative disorder that affects not only the patient but their family and caregivers. Both motor and non-motor symptoms are experienced and can have a significant effect on a patient's well-being and quality of life. There is currently no cure, so managing the symptoms are foremost in order to sustain a healthy well-being in these patients. The non-motor symptoms, especially cognitive decline, in PD are common and as PD is a continually evolving disorder, treatments need to be consistently re-assessed for accurate management.

Cognitive decline affects many patients with PD and can have a significant impact on quality of life with approximately 80% of people progressing to PDD within 20 years of disease diagnosis (Hindle et al., 2013). The rate of progression to PDD is remarkably heterogenous, as some patients remain relatively stable throughout their clinical course, whereas others develop complications early and at a faster rate (Greenland et al., 2019). It is therefore pertinent to have indicators of progression to PDD, particularly EEG markers that could be used to characterise cognition in the future.

Chapter 3: Electroencephalography in Parkinson's disease

3.1 Electroencephalogram

The electroencephalogram (EEG) has existed for over 100 years but equipment, data recording software, and analysis have been improved significantly over the last decade. The discovery of electrical currents in the brain was first made in 1875 by English physician, Richard Caton, using the exposed brains of monkeys and rabbits (Teplan, 2002). EEG recordings change with the functional status of the brain, including when the participant is sleeping, completing tasks in different states of alertness, and most obviously in neurological disorders such as epilepsy (Bronzino, 1995). In 1934, Adrian and Mathews verified the concept of human brain waves. They identified a brain wave that was a regular occurrence around 10-12 Hz which they named the 'alpha rhythm' (Bronzino, 1995). This frequency band and others have proven important in current research to detect changes in brain activity using EEG, including patients with cognitive impairment.

Electroencephalography has now become a routine neurophysiological imaging technique. It is low cost and non-invasive and measures electrical activity from the brain on the scalp (Al-Qazzaz et al., 2014; Babiloni et al., 2011; Bridwell et al., 2018). The development of EEG caps has improved the placement of electrodes and has reduced the time needed to collect data. The EEG works by measuring the electrical activity of neurons from the cortical surface of the brain via electrodes placed on the scalp. The EEG measures currents originating in the cerebral cortex during synaptic excitations of the dendrites of many neurons (Teplan, 2002). The electrical activity measured is voltage units from each EEG electrode reveals amplitudes up to 100 μV in human adults. Conductive gel is usually used to fill the gap between the electrodes and a participant's scalp to form a low impedance electrical connection. Brain activity can be recorded using EEG, which can also include abnormal brain activity. This is usually collected either when a person is completing a task, such as recognising visual items, or during resting wakefulness.

The EEG has many applications, including helping in the diagnosis of epilepsy and origins of epileptic activity, head injury, brain tumours and sleep problems (Hughes

& Melyn, 2005; Prigatano, Stahl, Orr, & Zeiner, 1982). The rest of this chapter is divided into two sections. The first part of this chapter focuses on general EEG concepts. The second part focuses on the EEG literature in relation to PD.

3.2 Advantages and disadvantages of the EEG

There are both advantages and disadvantages in the EEG regarding data collection and analysis. The main advantage is that EEG has the ability to monitor brain activity in real time with high temporal-resolution in the order of milliseconds; it is one of the few techniques that can acquire data to that level of temporal-resolution (Gavaret, Maillard, & Jung, 2015; Hämäläinen, Hari, Ilmoniemi, Knuutila, & Lounasmaa, 1993). As EEG is able to acquire data with a high temporal resolution, it can provide a unique insight into cognitive events that might otherwise be indistinguishable using techniques that have high spatial resolution but suffer from a low temporal resolution such as fMRI (Erickson, Kappenman, & Luck, 2018). For example, EEG can provide insight into how specific cognitive processes are affected in mental illnesses including schizophrenia, depression and anxiety (Erickson et al., 2018). High temporal resolution is also beneficial for neurological conditions and used in clinical settings to investigate and identify abnormal brain activity as well as determining accurate diagnosis and treatment (Haloi, Chanda, & Hazarika, 2019). Other advantages of the EEG are that it is silent and does not aggravate anxiety or claustrophobia, unlike fMRI and PET scans.

One of the main disadvantages of the EEG is its low spatial resolution (Burle et al., 2015). It has been hypothesised that volume conduction may be the main cause of poor spatial resolution (Burle et al., 2015). Moreover, the time taken to attach the electrodes prior to recording can be substantially long. This is because the EEG requires careful placement of electrodes on the head and applying conductive gel to establish an electrical connection between the electrodes and the scalp. This can take a considerably longer time than other techniques, although methods such as dry electrodes, that do not require gel to form a connection, can be used to reduce the time taken to connect the EEG cap.

3.3 The Resting State

Resting state reflects spontaneous neural activity that is elicited when a participant is awake but resting and not performing an explicit task (Greicius, 2008). It is being increasingly applied to study EEG from patients with neurological disorders including AD and PD (Babiloni et al., 2017b; Babiloni et al., 2016). The resting state is measured over a short period of time in which participants are asked to relax with their eyes closed but remain awake. The resting state can also be elicited in an eyes-open condition (Railo et al., 2020). Other techniques, including fMRI, can also be used to measure resting state brain activity, although there is the potential for the participant to feel claustrophobic (Hadidi et al., 2014). As the EEG is low cost, this makes multiple EEG recordings more feasible and can also be repeated over shorter periods of time to observe the trajectory of disease changes without any risks to the participant or researcher (Caviness et al., 2015). As there are no risks with repeated recordings, this makes EEG a valuable method for collecting longitudinal data in patients.

The data collected in EEG sessions are separated into frequency bands that represent the main spectrum of neural-derived oscillations in the brain. These brain waves are generally separated into five main frequency bands (Teplan, 2002). These are: delta (0.5-4 Hz), theta (4-8 Hz), alpha (8-12 Hz), beta (13-29 Hz), and gamma (30-80 Hz) (Cozac et al., 2016). Delta and theta can occasionally be seen during normal wakefulness, although usually these waves only become prominent during drowsiness (Louis & Frey, 2016). The alpha band is prominent when subjects have their eyes closed during resting wakefulness, usually observed in the posterior regions of the brain (Baars & Gage, 2013; Louis & Frey, 2016). The alpha wave is sometimes split into alpha low (alpha 1: 8-10 Hz) and alpha high (alpha 2: 10-12 Hz) (Cozac et al., 2016). The beta and gamma frequencies and are the fastest of the five bands (Kropotov, 2009). Beta waves are dominant during a normal state of active wakefulness (Teplan, 2002). The beta wave is most evident frontally and dominates our normal waking state of consciousness when attention is directed to a cognitive task (Kropotov, 2009). The gamma wave is the fastest of the brain waves and is often difficult to record due to noise artefacts seen above 50 Hz (Kropotov, 2009). Gamma is modulated by sensory input and internal processes such as working memory and attention (Jia & Kohn, 2011). These

frequency bands are often used to assess both spectral power and functional connectivity differences (Caviness et al., 2016; Chaturvedi et al., 2019).

3.3.1 Spectral Power and Individual Alpha Frequency (IAF)

Spectral analysis is a process used to quantify the EEG signal into its respective frequency bands. It measures the amplitude of the neuronal oscillations and denotes where an oscillation is in its cycle (Chaturvedi et al., 2019). Relative spectral power, also known as percentage power, is used to assess the contribution of a frequency to the EEG signal and is calculated by dividing the absolute power in each frequency band by the total power. This is often used to remove any potential between-subject differences. As relative spectral power is the proportion of power in each band, it is less confounded by inter-subject variability. Previous studies have investigated spectral power to determine frequency band differences in neurodegenerative disorders, including PD (Babiloni et al., 2011; Chaturvedi et al., 2019; Hogan, Swanwick, Kaiser, Rowan, & Lawlor, 2003; Utianski et al., 2016).

The individual alpha frequency (IAF), also known as the peak alpha frequency, is the dominant frequency recorded by EEG when the participant is in a state of resting wakefulness (Grandy et al., 2013). Previous studies have suggested that IAF is a stable neurophysiological marker and found that IAF is correlated to a person's mental health and cognitive functions (Grandy et al., 2013). In healthy controls, IAF may be useful as a marker for cognitive performance and is, for example, associated with training-related gains in cognitive tasks (Grandy et al., 2013).

3.3.2 Functional Connectivity

Functional connectivity has been used to describe the inter-dependency of electrical activity recorded from every pairs of electrodes for specified brain regions (Arroyave et al., 2019; Ponsen, Stam, Bosboom, Berendse, & Hillebrand, 2012). These measures including coherence, phase lag index (PLI), and weighted phase lag index (wPLI), can be used to analyse the phase synchrony and its strength between brain regions (Stephan, Friston, & Squire, 2009; Stoffers et al., 2008). It is not directional as it does not attempt to exploit prediction in time to infer effective (i.e., directional) connectivity. Normally, cognitive function relies on the coordination and integration of neuronal activity in

distinct brain regions (Boon, Hillebrand, Olde Dubbelink, Stam, & Berendse, 2017). Statistical dependencies derived from interactions between brain regions are between spatially distributed time series of neuronal activity (Boon et al., 2017). Functional connectivity has been studied using various types of imaging such as EEG, MEG, and fMRI.

Coherence measures the strength of the correlation between two signals across frequencies, quantifying the amount of dispersion of phases and amplitudes of the signals in a specific frequency width (Bowyer, 2016). Similar to other functional connectivity measures, coherence is often used with EEG measures to assess how connected specific locations in the brain are networked together (Bowyer, 2016). Although coherence is commonly used to measure functional connectivity, it is highly prone to volume conduction artefacts (Bowyer, 2016). Volume conduction refers to appearance of the activity of a source in the brain on multiple electrodes (Bastos & Schoffelen, 2015). This is specifically important in EEG, as coherence measures may therefore reflect spurious functional connectivity (Bastos & Schoffelen, 2015).

The phase lag index (PLI) is another tool to estimate connectivity in EEG, where the volume conduction effects are minimised. PLI is a more sensitive measure than coherence but in the calculation of PLI, only the phase (i.e., but not the amplitude) of the cross-power spectrum enters the analysis. It produces values between regions that range between 0 and 1, with 1 indicating perfect phase locking. The PLI also measures consistency across time and is robust to scalp volume conduction, which is a commonly reported issue with EEG recordings (Mehraram et al., 2020). However, PLI is sensitive to phase perturbations, since the amplitude of the signal is discarded (Vinck, Oostenveld, van Wingerden, Battaglia, & Pennartz, 2011).

The weighted phase lag index (wPLI) is a functional connectivity measure that is resistant to volume conduction and improves upon PLI by using a phase-difference weighting normalization (Lau, Gwin, McDowell, & Ferris, 2012; Mehraram et al., 2020; Vinck et al., 2011). WPLI has been shown to detect more complex and variable activity patterns than traditional voltage-amplitude measures (Lau et al., 2012) and it extends the PLI by additionally accounting for the magnitude of the phase difference (Hardmeier et al., 2014). It has also been reported to be less sensitive than PLI to

additional noise sources and has increased statistical power to detect changes in phase-synchronisation (Hardmeier et al., 2014; Vinck et al., 2011). Similar to PLI, the wPLI is bounded between 0 and 1, with 1 indicating full synchronisation (Mehraram et al., 2020). However, the wPLI is prone to sample-size bias which occurs when the population parameters have to be estimated from only a relatively small number of trials (Vinck et al., 2011). To overcome the sample-size bias, a debiased estimator of the squared wPLI was developed to help minimise the effect of the bias by removing the type of bias that is inherent to PLI (Vinck et al., 2011). As the debiased estimator is a weighted statistic, is itself unfortunately affected from an additional source of bias, denoted the 'weighting bias'. This is caused by the weights determining their own weight normalisation. However, Vinck et al. (2011) reported that the weighted bias is relatively unproblematic. A recent study has used wPLI to look at the difference between AD, dementia with Lewy bodies (DLB), PDD, compared to a HC group (Mehraram et al., 2020). This study reported that connectivity strength was lower in the AD, DLB, and PDD group, compared with the HC group in the alpha band, and the DLB group also had lower connectivity compared with AD group in the beta band. No significant differences between groups was found in the theta band. However, to the best of the author's knowledge, debiased wPLI (dwPLI) has not been investigated in PD.

3.4 Event-related Potentials (ERPs)

An ERP is a non-invasive way to measure brain response that is the result of a sensory, cognitive or motor event (Blackwood & Muir, 1990). It is a significant fluctuation in voltage that results from neural activity that has been evoked by an external stimulus (Picton et al., 2000). ERPs provide an interesting method to look at cognitive processes in neurodegenerative diseases and many other neurological or psychiatric disorders (Picton et al., 2000).

There are many different ERP components including N100, N200, P200 and P300. These components are identified based on positive or negative peaks of ERPs and their corresponding latency. ERP components are usually evaluated according to their amplitude and latency across many trials and are thought to represent the total activity of postsynaptic potentials when many similar neurons fire at once during information processing in the brain (Coles & Rugg, 1995; Peterson, Schroeder, & Arezzo,

1995). The latency of a component is measured in milliseconds from the onset of stimulus (Sur & Sinha, 2009). The amplitude of a component is measured in microvolts and is taken as the highest peak of an ERP component. The data are noisy due to the larger amplitude background brain activity present in the EEG (Coles & Rugg, 1995). An averaging process across many trials is intended to cancel out this noise.

The first ERP component to is the N100, which is a negative peak seen approximately 80-120 ms after the onset of a stimulus. It is commonly observed when an unexpected stimulus is presented to the patient and frequently produces the strongest amplitude at the central electrode Cz. This peak is the first of the four main peaks seen in a standard EEG response (Sur & Sinha, 2009). The P200 is the next wave in the sequence which is a positive peak at approximately 100-250 ms after the onset of a stimulus. The P200 has previously been thought to modulate perceptual processing and signify attentional recruitment (Sur & Sinha, 2009). The N200 wave appears after the P200 peak and is a negative peak seen approximately 200 ms after the onset of a stimulus. It is typically evoked before the motor response to the stimuli, indicating a possible link to the cognitive processes of stimulus identification (Patel & Azzam, 2005).

The P300 is the most commonly studied ERP and is most relevant to this thesis. It was discovered in the 1960s by Sutton, Braren, Zubin, and John (1965). It is a positive component of an ERP which peaks at approximately 300 ms, although can vary between 200-900 ms, after the presentation of a stimulus (Linden, 2005). The P300 amplitude has been found to increase with lower probability and higher discriminability of the target, although it is also found in response to the distractor and standard stimuli (Squires, Squires, & Hillyard, 1975). The target is explicitly determined to be infrequent which forces the participant to pay attention to each presented stimulus. This can, in turn, provide a more accurate measure of P300 if the target stimulus is rare (Linden, 2005). The P300 latency is also the other important component of the ERP that is commonly measured, and it has been previously noted that prolonged latencies are associated with lower cognitive performance (Sur & Sinha, 2009).

The P300 is associated with many cognitive processes such as attention, working memory, and decision making (Linden, 2005). It is also an important measure of dysfunction in neurological conditions (Linden, 2005). It is frequently elicited through

an auditory or visual oddball paradigm and thought to reflect processes involved with evaluation of a stimulus or categorization of that stimulus. Two types of P300 are elicited in a three-stimulus oddball task, which are tasks that include an infrequent distractor stimulus in addition to the target and standard stimuli. These two P300 ERPs are the P3a and P3b. The P3a is associated with the distractor stimuli and P3b is associated with the target stimuli (Linden, 2005). Polich (2007) suggests that the P3a originates from frontal attention mechanisms that are stimulus-driven during task processing. P3a amplitude is associated with attentional and executive function in PD (Seer, Lange, Georgiev, Jahanshahi, & Kopp, 2016). The P3b originates from activity in the temporal-parietal region (Polich, 2007). P3b latency is commonly associated with general cognitive impairment and suggested to be a promising tool to quantify general cognitive impairment in PD (Seer et al., 2016). More detail on the oddball task is provided below.

3.5 The Oddball Paradigm

As indicated, the (Coles & Rugg, 1995) oddball paradigm commonly includes a very low-probability stimulus (the target) and a high-probability (standard) stimulus. Generally, the participant is required to respond to the very low-probability target stimulus while ignoring the high-probability standard stimulus. (Huang, Chen, & Zhang, 2015; Smith, Donchin, Cohen, & Starr, 1970). There are different variations of the oddball task that studies have used over the last few decades (Seer et al., 2016). The most common is the basic two-stimulus oddball task which requires the participant to respond to an infrequent stimulus while ignoring a frequent stimulus (Green et al., 1996; Seer et al., 2016; Tanaka et al., 2000). This task can either be visual or auditory. In an auditory task there are infrequent tones that the participant is usually required to count throughout the task. In a visual task, the participant is usually required to press a button or click a mouse when they see an infrequent stimulus. Three-stimulus oddball tasks add a third stimulus and can again be either visual or auditory (Ozmus et al., 2017). The third stimulus is an infrequent non-target stimulus. The participant is generally required to respond only to the infrequent target stimulus.

Figure 3.1 illustrates an example of a three-stimulus visual oddball paradigm which has two counterbalanced subtasks: a circle and square task (Bocquillon et al., 2012). The participant is required to respond as fast as possible to the target stimulus

only, which is either a small circle or square, and ignore a larger distractor and standard stimulus. The shapes are displayed in a semi-random order for 75 ms each. The probability of seeing either the rare target or rare distractor stimulus is 8% and the probability of seeing the common standard stimulus is 84% (Bocquillon et al., 2012). The ISI in

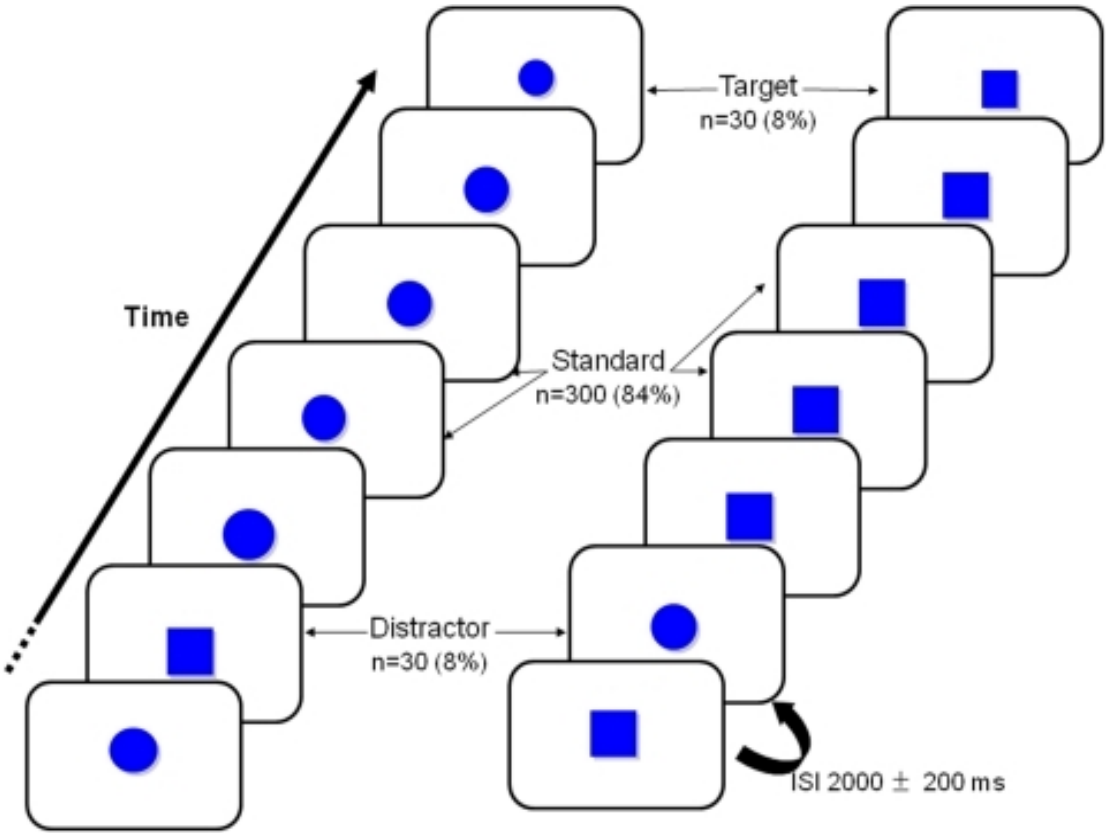

Figure 3.1 A schematic visual representation of a 3-stimulus visual oddball paradigm ((Bocquillon et al., 2012); doi:10.1371/journal.pone.0034239.g001).

this example is 2000 ± 200 ms and the total number of stimuli displayed in the experiment is 360. The oddball task used in this PhD was modelled off this task (Bocquillon et al., 2012).

3.6 Other Task-Based Paradigms

Aside from these oddball tasks, other paradigms used in ERP studies include mismatch negativity (MMN) and go/no tasks. MMN is a component of an ERP to an infrequent stimulus in a sequence of presented stimuli and has most frequently been studied using auditory stimuli (Rollnik, 2019). It is usually an auditory ERP that occurs when a sequence of repetitive sounds is interrupted by an occasional sound that differs in

frequency or duration. Note, in this instance the ERP is elicited regardless of whether the participant is paying attention to the sequence or not. In the go/no go task, participants are asked to respond to certain stimuli only and refrain from responding to other stimuli (Gajewski & Falkenstein, 2013). This task is similar to the two-stimulus oddball task, however the difference between the two tasks is that the target probability differs between these paradigms (i.e., frequent vs. rare, respectively). The go/no go task can measure information processing and decision making in participants (Goldstein & Naglieri, 2011). However, by far the most common task used is the oddball task (Seer et al., 2016).

3.7 The EEG in Parkinson's disease

The EEG has been used to investigate brain activity in PD, particularly to investigate cognitive decline and progression to PDD (Hunerli et al., 2019; Olde Dubbelink et al., 2013). PD is commonly associated with cognitive impairment, with up to 80% of people diagnosed with PD progressing to dementia over the course of their disease (Chaudhuri & Schapira, 2009). PD-MCI is used to identify those with PD whose cognitive ability is less than expected for their age; these patients are at increased risk of progression to PDD (Hoogland et al., 2017; Weil et al., 2018). EEG measures in PD patients who are cognitively impaired, i.e. those who meet criteria for PD-MCI or PDD, may suggest markers for early cognitive decline (Benz et al., 2014). This area of research is becoming more widely acknowledged due to the recent identification that PD is associated with non-motor symptoms that may even be present before the patient has been diagnosed (Poewe, 2008). Recent studies have also begun to investigate whether there is any relationship between evoked potentials elicited during a task and cognitive impairment, using cognitive tasks such as the oddball paradigm (Bocquillon et al., 2015; Tanaka et al., 2000). Therefore, using EEG to assess the brain activity of these individuals can help us to understand more about the complexity and progression of the disease.

A recent review highlighted the disruption of functional connectivity in patients with PD as well as the potential neurophysiological mechanisms underlying PD symptoms (Gao & Wu, 2016). This review was conducted to identify mechanisms of anti-parkinsonian interventions, and suggested that techniques, including EEG, have the potential to be used to identify biomarkers for the diagnosis of PD in the future. The

development of advanced EEG analysis tools has also enhanced the ability to evaluate functional neural networks at different spatial and temporal resolutions.

The participants in the following studies for the resting state and oddball paradigm have been characterised as either (1) PD, participants who are non-dementing and who are unclassified PD-N and PD-MCI patients, none of whom met the criteria for PDD, (2) PD-N who have relatively normal cognition and do not meet NZBRI Level II PD-MCI criteria, (3) PD-MCI, who meet the MDS Level II PD-MCI criteria using ten sensitive tests outlined by Myall et al. (2020) which identify PD-MCI patients who are at high relative risk of conversion to PDD in the next four years, and (4) PDD, those who meet criteria for PDD.

3.7.1 Resting State EEG in Parkinson's disease

Resting state activity in the brain is spontaneous but exhibits spatial and temporal organisation (Huang, 2019). It is also beneficial to help map out intrinsic connections in the brain to understand the disease progression and ultimately help understand the underlying functional changes. Resting state functional connectivity has been identified as associated to the motor system, the language system, executive control, and the dorsal and ventral attention systems (Britz, Van De Ville, & Michel, 2010). Table 3.1, Table 3.2, and Table 3.3 outline the research studies that have investigated the resting state using, IAF, spectral power and functional connectivity measures in PD. The criteria used to characterise cognition varies substantially in these tables and include the MDS Task Force criteria, and various neuropsychological tests (Dubbelink et al., 2013).

3.7.1.1 Individual Alpha Frequency and Spectral Power in PD

Currently only three studies have examined the relationship between IAF and cognition, especially in neurodegenerative diseases such as PD (Babiloni et al., 2017a; Babiloni et al., 2017b; Olde Dubbelink et al., 2013). However, none of these studies make direct comparisons between the full spectrum of cognition of HC, PD-N, PD-MCI, and PDD.

Two separate studies, albeit from the same research group, classified their participants as PD-MCI and PDD, but direct comparisons between these two groups were not made (Babiloni et al., 2017a; Babiloni et al., 2017b). Each of these two studies compared the PD groups (i.e. PD-MCI and PDD) with corresponding Alzheimer groups (i.e. AD-MCI and AD, respectively). (Babiloni et al., 2017a; Babiloni et al., 2017b).

The third study assessed cognitive function using the Cambridge Cognitive Examination (CAMCOG) (Olde Dubbelink et al., 2013). The CAMCOG is a standardised instrument used to measure the extent of dementia, and to assess the level of cognitive impairment (Roth, Tym, Mountjoy, Huppert, Hendrie, Verma, et al., 1986). The sample sizes for the PD groups in these three studies ranged from 42 to 75 participants.

Babiloni et al. (2017b) compared resting-state (eyes-closed) EEG in AD-MCI and PD-MCI. Their results showed that the mean IAF was higher in the healthy controls than both AD-MCI and PD-MCI groups. IAF was also higher in the AD-MCI group compared to the PD-MCI group. These IAF values were used as EEG landmarks to determine the frequency band ranges. The IAF was computed for each participant in the study and based on the IAF, the band range for each subject was estimated for the delta, alpha1, alpha2 and alpha3 frequency band ranges.

The second study by Babiloni et al. (2017a) compared IAF in patients with ADD, PDD, DLB, and healthy controls. They reported that the mean IAF was highest in the healthy control group and the PDD and DLB had the lowest IAF value. IAF was higher in the ADD group compared to the PDD and DLB and was lower in the ADD group compared to the HC group.

The third study to investigate IAF in PD used magnetoencephalogram (MEG) to examine changes over 4 years in "non-dementia" PD patients (Olde Dubbelink et al., 2013). They reported that IAF remained unchanged in the healthy controls, but IAF declined in the PD patients and this was associated with global scores on the Cambridge Examination Score. It was not clear if this association concerned baseline or follow up cognitive scores.

Similar to IAF, there is limited literature that has investigated spectral power group differences across frequency bands in PD (Bousleiman et al., 2014; Caviness et al., 2007; Fonseca, Tedrus, Carvas, & Machado, 2013; Fonseca, Tedrus, Letro, & Bossoni, 2009; Han, Wang, Yi, & Che, 2013). All of these studies found an increase in spectral power in the theta band and a reduction in the alpha band for cognitively impaired participants, i.e. those who met criteria for PDD or PD-MCI compared to non-demented PD participants (Bosboom et al., 2006; Bousleiman et al., 2014; Caviness et al., 2007; Chaturvedi et al., 2019). Despite similar findings, the participants in these studies differed substantially. Some studies compared spectral power differences using a PD group defined as 'non-dementing' which presumably included unclassified PD-N

and PD-MCI patients, none of whom met the criteria for PDD (Bosboom et al., 2006; Fonseca et al., 2013; Han et al., 2013; Ponsen et al., 2012). Others explicitly compared PD-N and PD-MCI groups, using various methods of characterising PD-MCI, including MDS-Task Force criteria and MMSE scores (Bousleiman et al., 2014; Caviness et al., 2007; Chaturvedi et al., 2019). In addition, several studies reported an increase in spectral power in the theta band, in patients classified as PDD, compared to a non-demented PD group that have not been classified on the basis of PD-N or PD-MCI (Bosboom et al., 2006; Ponsen et al., 2012). Furthermore, Han et al. (2013) compared a group of PD patients who had not been classified based on PD-N or PD-MCI criteria and compared them with a HC group to find that the non-demented PD group had an increase in power in the delta and theta band, and a decrease in power in the alpha band.

Currently there is only one study that makes a comparison between a PD group, who were not classified on the basis of PD-N or PD-MCI, and a HC group (Han et al., 2013). This study found that there was an increase in power in the delta and theta band, and a decrease of power in the alpha and beta band in PD patients compared with HCs. There are another three studies that have looked at a variety of group comparisons in the PD literature, and compared group differences between 'non-demented' PD patients, i.e., were not classified on the basis of PD-N or PD-MCI criteria, and PD patients who met criteria for PDD (Bosboom et al., 2006; Fonseca et al., 2013), with only one of these studies not including a comparison between a HC group (Ponsen et al., 2012). Bosboom et al. (2006) reported that in the non-demented PD patients, theta power was increased, and beta power was decreased relative to HCs. In the PDD patients, an increase in the delta band and a decrease in alpha band was reported in comparison to the non-demented PD group. Similarly, Fonseca et al. (2013) compared a non-demented PD, PDD, ADD, and HC group to determine spectral power differences. This study found that delta and theta powers were highest in the PDD group and lowest in the HC group. Furthermore, there were no significant differences between groups for the alpha and beta band. Lastly Ponsen et al. (2012) compared a non-demented PD group with a PDD group and found that compared to PD patients, PDD patients had more delta and theta power, respectively. The PDD patients also had less alpha and beta power, respectively.

Another three studies looked at group comparisons between non-demented PD and PD-MCI patients, with one of the three studies including a comparison between a

PDD group as well (Bousleiman et al., 2014; Caviness et al., 2007; Chaturvedi et al., 2019). None of the three studies included a HC group as a baseline in their comparisons. Chaturvedi et al. (2019) investigated group differences between a PD-N and PD-MCI group which were classified based off the Litvan et al. (2012) Level II criteria. This study aimed to determine whether spectral power could be used to identify patients with mild cognitive impairment in PD. Their study found an increase in spectral power in the frequency range below 8 Hz and a decrease in spectral power above 8 Hz, indicating a risk of cognitive decline in PD (Chaturvedi et al., 2019).

Another study investigated spectral power to screen patients with parkinsonian symptoms for mild cognitive impairment, again making comparisons between a PD-N and PD-MCI group (Bousleiman et al., 2014). This study also classified their participants off MDS Task Force guidelines for the diagnosis of PD-MCI. They found that lower mean spectral power values were observed in the alpha band for the PD-N group compared to the PD-MCI group in the frontal, central, temporal, and occipital regions. They also showed the large effect sizes of these differences.

The third study made a group comparison between a non-demented PD, PD-MCI and PDD group (Caviness et al., 2007). A status of PD was established by no evidence of cognitive impairment, whereas a PD-MCI diagnosis was achieved by using the MDS Level I criteria where at least 1.5 SD below age corrected mean score on at least one neuropsychological test. Lastly the PDD diagnosis was classified if the DSM-IV criteria for PDD was met. This study found that PD-MCI exhibited higher delta and theta power and lower alpha power than the non-demented PD group. The PDD and PD-MCI group did not differ in the theta or beta bands, but non-demented PD had higher delta and lower alpha power than the PD-MCI group.

To our knowledge, only two studies have investigated spectral power differences in PD across the full spectrum of cognition, comprising a healthy control, PD-N, PD-MCI, and PDD groups (Caviness et al., 2016; Fonseca et al., 2009). The results for these two studies also follow the same trend as above of an increase in spectral power in the theta band for the PD-MCI group compared to the PD-N group and a decrease in alpha band spectral power for the PDD group (Caviness et al., 2016; Fonseca et al., 2009). Fonseca et al. (2009) compared spectral power group differences in the fronto-temporal and posterior regions, whereas Caviness et al. (2016) looked at global relative power for each frequency band and did not define any regions of interest in their study.

However, Fonseca et al. (2009) had a relatively small sample size (N = 58), especially for their PD patients and classified their patients cognition using a neurological examination combined with the CERAD neuropsychological, CDR, and Hoehn and Yahr scale. Caviness et al. (2016) on the other hand had a larger sample size, although they classified their patients' cognitive status using the MDS Level I criteria which is not as reliable as the recently published criteria by Myall et al. (2020).

Spectral power and IAF are important measures to determine relevant changes between cognitive groups in PD. Posterior changes have been observed in the brains of patients with PD who rapidly declined to PDD (Kehagia et al., 2013). Analysing spectral power and IAF across cognitive groups in PD may help us to determine markers to characterise cognition in participants. In addition to finding a marker for cognition, using spectral power and IAF in combination with other techniques, such as functional connectivity may be beneficial to analyse regional changes in the brain, as well as alterations to the synchrony between regions. In turn, these measures might also be used to assist in time-efficient characterisation of cognitive status in PD, as well as monitor changes in cognition in a follow up longitudinal study. Table 3.1 and Table 3.2 summarise the main spectral power and IAF findings in the PD literature.

Table 3.1 PD studies on IAF in the resting state using EEG.

Reference	Participants	Time since disease onset (years)	Regions used for analysis	Task Used/Criteria for classification of cognitive status	Main Findings
Babiloni et al. (2017b)	HC = 75 AD-MCI = 75 PD-MCI = 75	NA	Frontal, Central, Parietal, Temporal, Occipital	Eyes-closed resting state condition. AD-MCI was diagnosed by a MMSE ≤ 24, CDR score of 0.5, logical memory test score of 1.5SD below age-adjusted mean, and GDS sore ≤ 5. PD-MCI was based on the Litvan et al. (2012) criteria.	They looked at IAF, and reported group differences between patients with ADD, PDD, DLB, and healthy controls. (HC > AD-MCI > PD-MCI). IAF was highest in the healthy control group and the PDD and DLB had the lowest IAF value.
Babiloni et al. (2017a)	ADD = 42 PDD = 42 DLB = 34 HC = 40	NA	Left and right for the frontal, central, parietal, occipital, and temporal	Eyes-closed resting state condition. ADD was diagnosed according to the criteria of the (DSM-IV-TR) and the National Institute of Neurological Disorders and Stroke Alzheimer Disease and Related Disorders. PDD was diagnosed using a battery of clinical scales including the Neuropsychiatric Inventory, the scale of assessment of behavioural and psychological symptoms of dementia, the MMSE, the dementia rating scale-2, and a battery of neuropsychological tests.	Mean IAFs were 9.0 Hz in HC subjects, 8.0 Hz in ADD patients, 7.3 Hz in PDD patients, and 7.2 Hz in DLB patients. (HC > ADD > PDD > DLB). The mean IAF was greater in HC than ADD, PDD, and DLB patients. Also higher in ADD than in PDD and DLB groups.

Olde Dubbelink et al. (2013)	HC = 14 PD = 43	PD = 5.35	Occipital	Eyes-closed resting state condition. Global cognitive function and presence of dementia was assessed using the Cambridge Cognitive Examination.	This was a longitudinal study over 4 years. In contrast to healthy controls, PD patients showed a slowing of the dominant peak frequency (IAF). (HC > PD). HC IAF remained relatively similar at baseline and follow up whereas the PD group had lower IAF on average compared to their baseline IAF.

Abbreviations: ADD = Alzheimer's disease with dementia; DLB = Dementia with Lewy bodies; EEG = Electroencephalogram; HC = Healthy controls; IAF = Individual Alpha Frequency; MEG = Magnetoencephalography; NA = Not available; PDD = Parkinson's disease with dementia; PD = non-demented Parkinson's disease that have not been classified on the basis of PD-N or PD-MCI; QEEG = Quantitative Electroencephalogram.

Table 3.2 PD studies on spectral power in the resting state using EEG.

Reference	Participants	Time since disease onset (years)	Regions used for analysis	Task Used/Criteria for classification of cognitive status	Main Findings
Bosboom et al. (2006)	HC = 13 Non-demented PD = 13 Demented PD = 13	Non-demented PD = 9.69 Demented PD = 11.23	Ten regions of interest (frontal, central, temporal, parietal and occipital) on the left and right side	Eyes-closed resting state condition followed by an eyes-open resting state condition. Non-demented PD patients had a MMSE score of >28. Demented PD patients fulfilled DSM-IV criteria for dementia and had a MMSE of 24 or lower.	In the non-demented PD patients, relative theta power was diffusely increased, and beta power concomitantly decreased relative to controls. Gamma power was decreased in central and parietal channels. In the demented PD patients, a diffuse increase in relative delta and to a lesser extent theta power and a decrease in relative alpha, beta, and to a lesser extent gamma power were found in comparison to the non-demented PD group.
Ponsen et al. (2012)	Non-demented PD = 13 PDD = 13	Non-demented PD = 9.69 PDD = 11.2	34 regions of interest across the brain.	Eyes-closed resting state condition followed by an eyes-open resting state condition. Non-demented PD patients had a MMSE score of >28. Demented PD patients fulfilled DSM-IV criteria for dementia and had a MMSE of 24 or lower.	Compared to PD patients, PDD patients had more delta and theta power in parieto-occipital and fronto-parietal areas, respectively. The PDD patients had less alpha and beta power in parieto-temporo-occipital and frontal areas, respectively.

Fonseca et al. (2013)	AD = 38 PDD = 12 Non-demented PD = 31 HC = 37	NA	Frontal left–right; mid temporal left–right and occipital left–right.	Eyes-closed resting state EEG. AD used the DSM-IV criteria. PDD criteria used by Calne et al. (1992) and Dubois (2007). PD did not fulfil criteria for PDD.	The delta and theta powers were highest in PDD and lowest in CG. The beta frontal-occipital inter-hemispheric coherence was highest in PDD. Whereas alpha and beta frontal inter-hemispheric coherence was highest in PDD and lowest in AD.
Han et al. (2013)	HC = 15 PD = 15	Not specified	No regions specified	Eyes-closed resting state. Hoehn and Yahr and MMSE were used for each participant.	An increase of relative powers in the delta and theta band, and a decrease of relative powers in the alpha and beta band were observed for PD patients compared with controls.
Caviness et al. (2007)	PD = 42 PD-MCI = 16 PDD = 8	PD = 5.4 PD-MCI = 7.8 PDD = 10.7	Frontal, Central, Occipital and Parietal regions	Eyes-closed-resting state. PD-MCI: At least 1.5 standard deviation below age corrected mean score on at least one area of neuropsychological testing, dementia criteria not met. PD-D: DSM-IV criteria for dementia met. PD: A diagnosis of PD without evidence of cognitive impairment.	PD-MCI exhibited higher delta and theta band-power and lower alpha band-power than the PD group. PD-D and PD-MCI did not differ in the theta or beta bands, but PD-D had higher delta and lower alpha band power than the PD-MCI group. Parietal region EEG power showed a difference only in the delta band for PD-D vs. PD. In the group analysis, frontal region EEG power showed mean differences only in the theta band for PD-MCI vs. PD, delta band for PD-D vs. PD-MCI, and in the delta and theta bands for PD-D vs. PD.

Bousleiman et al. (2014)	PD-N = 12 PD-MCI = 41	Overall disease duration = 8.6	Frontal left, Central left, Temporal left, Temporal right, Occipital left	Eyes-closed resting state. PD-MCI was evaluated along the Movement Disorder. Society Task Force guidelines for the diagnosis of PD-MCI.	Lower mean values were observed for PD-MCI group compared with the PD-N group in global alpha1 power and alpha1 power in five brain regions (left hemisphere: frontal, central, temporal, occipital; right hemisphere: temporal. Effect sizes were high, ranging from 0.79 to 0.87. Median frequency was 8.56 ± 0.74 Hz and was not significantly different between the groups.
Chaturvedi et al. (2019)	PD = 43 PD-MCI = 27	PD = 4 PD-MCI = 5	Frontal left/right, central left/right, parietal left/right, temporal left/right, and occipital left/right	Eyes-closed resting state. PD characterised according to MMSE above 24. PD-MCI diagnosis was based on Litvan et al. (2012) level II criteria.	While inspecting the differences in the global EEG features in the two groups, relative median spectral power in theta and beta bands differed between PD-MCI and PD patient groups. Patients with PD-MCI, in comparison to those without MCI, had differences in the frequency measures: higher theta spectral power, and lower beta power.
Caviness et al. (2016)	Lewy Body disease = 13 PD = 75 PD-MCI = 28 PDD = 31 HC = 51	PD = 9.8 PD-MCI = 12.2 PDD = 14.7	No regions outlined	Eyes-closed resting state. Cognitive status was made in a consensus conference with movement disorder and cognitive neurologists and neuropsychologists. MDS guidelines were used for PD-MCI and PDD.	PD-MCI exhibited higher delta and theta band power and lower alpha band power than the PD group. PDD and PD-MCI did not differ in the theta or beta bands, but PDD had higher delta and lower alpha band power than the PD-MCI group.

Fonseca et al. (2009)	HC = 26 PD- N = 15 PD-MCI =10 PDD = 7	PD- N = 6.8 PD-MCI = 6.0 PDD = 8.7	Frontotemporal and Posterior	Eyes-open and eyes-closed resting state. A neurological examination, PD-MCI diagnosis was made corresponding to cognitive complaints from the patients or their families; the reporting of a relative decline in cognitive functioning during the past year by a patient or informant; cognitive disorders as evidenced by a clinical evaluation; absence of major repercussions on daily life; and absence of dementia.	An increase in the absolute and relative posterior theta amplitude in the groups with PD-MCI or PDD and of the posterior absolute and relative delta amplitude in the group with PDD.
Cozac et al. (2016)	Review Paper	-	-	Resting state (either eyes-closed or eyes-open). Each paper had their own classification criteria.	This review study looked at IAF and spectral power. They summarise several studies that have shown QEEG to be a promising predictor of PD-related cognitive decline. Twenty-four studies reported QEEG findings in various cognitive states in PD. Spectral and connectivity markers of QEEG could help to discriminate between PD patients with different level of cognitive decline.

Abbreviations: AD = Alzheimer's disease; AZSAND = Arizona Study of Aging and Neurodegenerative Disorders; DSM-IV = Diagnostic and Statistical Manual for Mental Disorders, Version 4; EEG = Electroencephalogram; HC = Healthy controls; NA = Not available; PD = non-demented Parkinson's disease that have not been classified on the basis of PD-N or PD-MCI; PDD = Parkinson's disease with dementia; PD-N = non-demented Parkinson's disease; PD-MCI = Parkinson's disease with mild cognitive impairment; MCI = Mild Cognitive Impairment; MEG = Magnetoencephalography; MMSE = Mini-Mental Score Examination; UPDRS = Unified Parkinson's Disease Rating Scale

3.7.1.2 Functional Connectivity in Parkinson's disease

Functional connectivity is another common EEG analysis that has been investigated in PD, with many studies looking at the association of resting state functional connectivity and cognition. Similar to spectral power, there has been a general trend that shows functional connectivity is reduced in the alpha band in patients who are cognitively impaired (Arroyave et al., 2019; Babiloni et al., 2018b; Bosboom, Stoffers, Wolters, Stam, & Berendse, 2009b; Chaturvedi et al., 2019; Olde Dubbelink et al., 2013; Ponsen et al., 2012; Utianski et al., 2016). Arroyave et al. (2019) included a PD-MCI group in their study and found that the PD-MCI group had lower functional connectivity in the delta band, compared with the HC and PD-N group, and higher functional connectivity in the theta band for the PD-MCI group compared to the PD-N group. Chaturvedi et al. (2019) also included a PD-MCI group and made group comparisons between a PD-N group. Similarly, they found that functional connectivity for the PD-MCI group was higher in the theta band, compared with the PD-N group.

Most studies have included PD patients of varying disease duration but most commonly refer to them as 'non-dementing' or 'early disease' and 'advanced disease' (Dubbelink et al., 2013; Teramoto et al., 2016). Others have included participants that meet criteria for PD-MCI and PDD, although these groups were often not directly compared with HC and non-impaired PD participants (Arroyave et al., 2019; Babiloni et al., 2018a; Chaturvedi et al., 2019). These studies have also looked at both eyes-closed and eyes-open resting-state functional connectivity in both on and off states of medication. They have also used various criteria to categorise their patients, including the Litvan et al. (2012) (Chaturvedi et al., 2019; Teramoto et al., 2016). Others have used a range of neuropsychological measures to match participants such as, MoCA, UPDRS and the MMSE (Arroyave et al., 2019; Babiloni et al., 2018b; Utianski et al., 2016). Studies have also used a clinical diagnosis of PD as their classification for cognitive status (Bertrand et al., 2016). To our knowledge there is only one functional connectivity study that has made a direct comparison between a HC, PD-N, PD-MCI and PDD group (Utianski et al., 2016). This study had a relatively large sample size, although they classified participants using UPDRS, MoCA and MMSE scores as opposed to recognised criteria for cognition such as the MDS Task Force criteria (Litvan et al., 2012). They

found that functional connectivity was lower in the PDD group in the alpha band, compared to the other three groups and concluded that these findings reveal several distinct patterns associated with cognitive decline in PD (Utianski et al., 2016).

An association between resting-state functional connectivity and cognitive decline in PD has been shown previously (Boon et al., 2017). This disruption in PD suggests an association between cognitive decline and loss of resting state functional connectivity in the alpha band in the frontotemporal region (Bosboom et al., 2009b). Another study investigated resting-state functional connectivity and reported that when comparing a PD group to a healthy control group, the PD group had higher functional connectivity in the theta and high beta bands in the frontal region (Moazami-Goudarzi, Sarnthein, Michels, Moukhtieva, & Jeanmonod, 2008). Another study compared PD participants who were not cognitively impaired with PDD and found that frontal and parietal delta and alpha band functional connectivity was lower in the PDD participants (Ponsen et al., 2012). Much of the above resting-state functional connectivity studies looked at PD participants with no cognitive impairment and compared them to healthy controls.

There are many functional connectivity measures that have previously been used in the resting state literature and may contribute to the different results found in previous studies. These measures include coherence, phase lag index (PLI), and weighted phase lag index (wPLI), which have been previously described in section 3.3.2. These aim to measure the strength of the correlations between two signals and analyse phase synchrony between brain regions. However, these methods have constraints and as a result may not be the best measures to use (Stephan et al., 2009; Stoffers et al., 2008). Coherence has previously been used in functional connectivity studies in PD to investigate potential markers for cognitive decline and progression to PDD (Arroyave et al., 2019; Babiloni et al., 2018b; Bertrand et al., 2016; Bosboom, Stoffers, Stam, Berendse, & Wolters, 2009a; Moazami-Goudarzi et al., 2008; Teramoto et al., 2016). However, coherence is highly prone to volume conduction and may introduce spurious connectivity (Bastos & Schoffelen, 2015). PLI is also commonly used in the PD literature and is another tool to estimate connectivity in EEG (Chaturvedi et al., 2019; Geraedts et al., 2018b; Hassan et al., 2017; Olde Dubbelink et al., 2013; Ponsen

et al., 2012; Utianski et al., 2016). PLI is more sensitive than coherence, however PLI is sensitive to phase perturbations (Vinck et al., 2011). WPLI extends from PLI, and aims to overcome these limitations, however, to our knowledge have not been used previously in the PD literature. WPLI is reported to be less sensitive to noise sources than PLI, although wPLI is prone to sample-bias (Vinck et al., 2011). To overcome this bias, a debiased estimator has been developed which is the chosen method for our study. This measure is affected by a weighting bias, although this bias has been reported to be relatively unproblematic (Vinck et al., 2011).

The main findings from the literature (Table 3.3) demonstrates that a decrease in resting state functional connectivity is related to cognitive decline and may be a potential marker for developing dementia.

Table 3.3 PD studies researching resting-state functional connectivity using EEG and MEG.

Reference	Participants	Time since disease onset (years)	Regions used for analysis and FC measure used	Task Used/Criteria for classification of cognitive status	Main Findings
Teramoto et al. (2016)	PD = 68	PD = 5	Frontal and Parietal FC measure: Coherence	Eyes-closed resting state condition. PD was assessed using the MMSE based on the DSM-IV for dementia, and patients with an MMSE score <24 were excluded.	Low EEG coherence between the left frontal and left parietal region was associated with poor executive task performance in PD. A decrease in resting state functional connectivity between the frontal and parietal cortices is related to executive function in PD.
Geraedts et al. (2018b)	PD = 63	PD = 11.9 (6.3 SD)	Frontal, Central, Parietal, Temporal and Occipital FC measure: PLI	Eyes-closed resting-state condition. Patients were classified using MDS-TF criteria.	In all instances, reduced functional connectivity in all frequency correlated with higher disease severity. Both EEG slowing and reduced functional connectivity in the alpha 2 band are associated with increased non-dopaminergic disease severity in PD, particularly with cognitive impairment. EEG alterations were apparent both globally and over separate brain regions. The parameters may have the potential to serve as biomarkers of disease severity in PD.
Moazami-Goudarzi et al. (2008)	PD = 24 HC = 34	PD = 9.6 HC = NA	Frontal, Central and Parietal FC measure: Coherence	Eyes closed resting state. Most patients displayed a combination of tremor and akinesia and there was no clinical evidence of dementia.	In the frontal region of interest, the PD group had enhanced coherence in the theta, high beta, and gamma frequency bands. In parietal regions of interest, PDs showed lower coherence compared to HCs.

Bosboom et al. (2009b)	Non-demented PD = 13 PDD = 13	Non-demented PD = 9.7 PDD = 11.2	Frontal, Central, Temporal, Parietal and Occipital FC measure: Coherence	Eyes closed resting state. PD patients did not experience difficulties with cognitive functioning in daily life and did not display any signs of dementia on clinical as well as neuropsychological examination. PDD was determined using the DSM-IV criteria for dementia.	There was a reduction in long-distance intrahemispheric, predominantly bilateral fronto-temporal synchronization in the alpha1 and alpha2 bands in demented patients, together with a reduction in intertemporal synchronization in the 0.5-10 Hz frequency range. Changes in functional connectivity have been reported in non-demented PD patients in several stages of disease.
Ponsen et al. (2012) (same participants as (Bosboom et al., 2009b))	Non-demented PD = 13 PDD = 13	Non-demented PD = 9.7 PDD = 11.2	68 regions of interest. FC measure: PLI	Eyes closed resting state condition followed by an eye open resting state condition. The participants were the same as Bosboom et al. (2009b).	Compared to non-demented PD patients, PDD patients had more delta and theta power in parieto-occipital and fronto-parietal areas, respectively. Compared to PD patients, PDD patients had lower mean PLI values in the delta and alpha bands in fronto-temporal and parieto-temporo-occipital areas, respectively. This study shows a widespread reduction in functional connectivity between different regions in PDD.
Bertrand et al. (2016)	HC = 37 PD = 44 PDD = 18	HC = NA PD = 3.51 PDD = 4.06	Posterior FC measure: Coherence	Eyes-closed EEG was performed at a minimum of 30 min after waking up in the morning. The MDS Task Force criteria were used to determine cognitive status for PD and the DSM-IV was used for dementia.	Increased variability/randomization of networks communication in low frequencies combined with hyper synchronization/loss of information processing in high frequencies were identified as potential predictive markers of dementia in PD. These findings suggest that specific disruptions of brain communication can be measured before PD patients develop dementia, providing a new potential marker to identify patients at highest risk of developing dementia.

Olde Dubbelink et al. (2013)	HC = 14 De novo PD = 12 PD baseline = 43 PD follow up = 43	HC = NA De novo PD = 0.92 PD baseline = 5.19 PD follow up = 9.56	Left and right for frontal, central, parietal, occipital and temporal FC measure: PLI	Eyes-closed resting state condition. Participants from Stoffers et al. (2007).	At baseline, early stage, untreated PD patients had lower para-hippocampal and temporal delta band connectivity and higher temporal alpha1 band connectivity compared to controls. Longitudinal analyses over a 4-year period in a larger patient group revealed decreases in alpha1 and alpha2 band connectivity for multiple seed regions that were associated with motor or cognitive deterioration. These changes in functional connectivity appeared to reflect clinically relevant phenomena and therefore hold promise as a marker of disease progression.
Hassan et al. (2017)	PD (G1) = 63 PD-MCI (G2) = 46 PDD (G3) = 15	PD = 8.05 PD-MCI = 8.8 PDD = 10.6	68 regions of interest FC measure: PLI	Eyes-closed resting-state condition. Groups were based on their score from a neuropsychological assessment. 1) cognitively intact patients (G1), 2) patients with mild to moderate deficits in executive functions (G2), 3) patients with severe cognitive impairment (G3).	There were progressive disruptions in functional connectivity between the three patient groups, typically in the alpha band. Differences between G1 and G2 were mainly frontotemporal alterations. These findings indicate that functional connectivity decreases with the worsening of cognitive performance and loss of frontotemporal connectivity may be a promising neuromarker of cognitive impairment in PD.
Babiloni et al. (2018b)	HC = 75 AD-MCI = 75 PD-MCI = 75	AD-MCI = NA PD-MCI = NA HC= NA	Frontal, Central, Parietal, Occipital and Temporal FC measure: Coherence	Eyes-closed resting-state condition. AD-MCI criteria was based off MMSE > 24 and CDR of 0.5. PD-MCI criteria was based off Litvan et al. (2012)	Posterior interhemispheric and widespread intrahemispheric alpha lagged linear connectivity (LLC) solutions were abnormally lower in both MCI groups compared to the HC group. No differences in the LLC solutions were found between the two MCI groups. These findings unveil similar abnormalities in functional cortical connectivity estimated in widespread alpha sources in AD-MCI and PD-MCI. The similar abnormality of alpha source connectivity in AD-MCI and PD-MCI subjects might reflect common cholinergic impairment.

Arroyave et al. (2019)	HC = 36 PD-N = 22 PD-MCI = 14	PD-N = 4.4 PD-MCI = 6.2	Left and right for the frontal, temporal, parietal and occipital FC measure: Coherence	Eyes-closed resting-state condition. Cognitive screening was performed using the MoCA. PD-N participants did not have any significant cognitive complaints and a MoCA score of >23. PD-MCI participants were classified using MDS Level I criteria and had a MoCA score of <23.	PD subjects without MCI (PD-N) had lower intra and interhemispheric coherence in alpha2 compared with controls. PD with MCI (PD-MCI) showed higher intra and posterior interhemispheric coherence in alpha2 and beta1, respectively, in comparison to PD-N. PD-MCI presented lower frontal coherence in beta frequencies compared with PD-N. EEG coherence measures indicate distinct cortical activity in PD with and without MCI.
Chaturvedi et al. (2019)	PD-N = 43 PD-MCI = 27	PD-N = 4 PD-MCI = 5	Left and right for the frontal, central, parietal, temporal and occipital FC measure: PLI	Eyes-closed resting-state condition. PD-MCI participants were diagnosed using MDS Level II criteria.	Functional connectivity measures- higher phase lag index for the PD-MCI group in the theta band. Phase lag index is an effective EEG measure to identify PD patients with PD-MCI.
Utianski et al. (2016)	HC = 57 PD-N = 57 PD-MCI = 13 PDD = 18	PD-N = 9.7 PD-MCI = 13.8 PDD = 17.0	No regions specified. FC measure: PLI	Eyes-closed resting state condition. MDS guidelines were used for PD-MCI and PDD participants.	Network measures showed increased local integration across all frequency bands between control and PD-N; in contrast, decreased local integration occurred in PDD when compared to PD-N in the alpha1 frequency band. Correlations were found between network measures and assessments of global cognitive performance in PD.

Abbreviations: AD-MCI = Alzheimer's disease with mild cognitive impairment; EEG = Electroencephalogram; HC = Healthy controls; Hz = Hertz; LLC = Lagged linear connectivity; MCI = Mild Cognitive Impairment; MEG = Magnetoencephalography; MoCA = Montreal Cognitive Assessment; MMSE = Mini-mental Examination; NA = Not available; PD = Parkinson's disease; PDD = Parkinson's disease with dementia; PLI = Phase lag index; PD-MCI = Parkinson's disease with mild cognitive impairment; PD-N = Parkinson's disease with no deficit.

3.7.2 The Oddball Paradigm in Parkinson's disease

There have been several studies over the past few decades that have investigated the oddball paradigm in the context of PD (Seer et al., 2016). These studies have used different variations of the oddball task, including visual, auditory and different stimulus versions (Bocquillon et al., 2015; Hunerli et al., 2019; Silva Lopes, Souza Melo, & Nobrega, 2014). There have also been studies that have used EEG to analyse oddball ERPs in varying levels of cognition in PD such as Toda, Tachibana, Sugita, and Konishi (1993) and more recently Hunerli et al. (2019). However, most of these studies focus on PD participants who have not met the criteria for PD-MCI (Bocquillon et al., 2012; Ozmus et al., 2017; Silva Lopes et al., 2014; Tanaka et al., 2000; Wang et al., 1999). Few studies have included patients who meet the criteria for PD-MCI and PDD, although the criteria used for classification varies across these studies (Hunerli et al., 2019).

Majority of the previous studies used the MDS Task Force criteria to characterise cognition, although other studies used MMSE and the DSM-IV criteria. Previous literature has investigated both two and three-stimulus visual and auditory oddball tasks to look for any differences between participant groups. This has been outlined by Seer et al. (2016), who conducted a review of studies that investigated ERPs and cognition in PD. This review outlined several studies that used either oddball tasks that had two or three stimuli and were either visual or auditory (Bocquillon et al., 2012; Fogelson, Fernandez-Del-Olmo, & Santos-Garcia, 2011; Green et al., 1996; Hozumi, Hirata, Tanaka, & Yamazaki, 2000). These studies report varying effects on the P300 amplitude and latency, which may be due to methodological differences including the methods used for classifying cognitive status (Bocquillon et al., 2012; Kaufman, Bowers, Okun, Van Patten, & Perlstein, 2016). However, to our knowledge, there are no previous studies that have investigated ERP differences in a HC, PD-N, PD-MCI and PDD group.

Of the studies which have looked at the three-stimulus visual oddball task in PD varying results have been reported (Kaufman et al., 2016; Toda et al., 1993). As shown

in Table 3.3, some studies reported no significant difference in the P300 amplitude or latency between the PD-N participants and HC participants. Although there were differences in reaction time between PD-N and HC participants, as the PD-N participants took longer to respond to the stimulus (Toda et al., 1993). This study also reported that when looking at the differences between the PDD and PD-N patients, the PDD patients had significantly longer P300 latency to HC and PD-N patients. In contrast, other studies have reported that the P300 amplitude was reduced when compared to HC participants (Hunerli et al., 2019). They also found that PD-MCI participants had lower amplitudes than both the PD-N and HC participants when completing a visual oddball task.

As mentioned, many studies have looked at various aspects of the P300 in PD, including P300 subcomponents P3a an P3b. These have been looked at to determine whether there are any differences between the amplitude and latency of these components, using different variations of the oddball task (Seer et al., 2016). The ERP responses for latency and amplitude are often taken from the P300 component and have previously been looked at in EEG studies to determine any difference between PD patients and healthy controls (Linden, 2005; Squires, Squires, & Hillyard, 1975; Sur & Sinha, 2009). A review by Seer et al. (2016) compiled all oddball task literature that included PD participants and looked at the P3a and P3b measures during the oddball paradigm in patients with PD. They found that, for both visual and auditory tasks, P3b latency was increased for PD patients compared to healthy controls, whereas no difference in amplitude between PDs and healthy controls was found for both the two and three stimulus versions. Although, when looking at the P3a latency and amplitude in a three-stimulus oddball task, overall, there was no difference in latency between PD participants and healthy controls. There was also a decrease in amplitude for the PDs compared to the healthy controls (Seer et al., 2016). They concluded that the majority of previous P3a and P3b literature was consistent across studies. These ERP measures may be used to assist, in combination with resting state measures, in the characterisation of cognitive status in PD. Table 3.4 outlines the major oddball studies that have been conducted and their findings.

Table 3.4 PD studies researching the oddball paradigm and ERPs.

Reference	Participants	Time since disease onset (years)	Average Age (years)	Task Used/Criteria for classification of cognitive status	Main Findings
Wang et al. (1999)	HC= 24 PD= 38	PD= 7.4	HC= 65.2 PD = 65.8	Three-stimuli visual oddball task (rare target, rare non-target, and frequent non-target). Event probabilities: rare target (20%), rare non-target (20%) and frequent non-target (60%). Patients were assessed using the DSM-III.	P300 latency was significantly delayed after rate target stimuli only at the long ISI in patients with PD compared to HCs. P300 amplitude to rare non-target stimuli in PD patients at all three ISIs was significantly reduced in comparison with HCs.
Bocquillon et al. (2012)	HC = 15 PD = 15	PD = 4.8	HC = 59.1 PD = 59.2	Three-stimulus visual oddball paradigm (target, distractor, and standard stimuli). Event probabilities: target (8%), distractor (8%) and standard stimuli (84%). Patients were classified using the DSM-IV criteria.	swLORETA analyses showed that PD patients displayed fewer dorsolateral prefrontal distracter P300 but no significant differences in target elicited P300 sources. The results suggest that the cortical attention fronto-parietal networks (mainly the dorsal one) are modulated by the basal ganglia. Disruption of this network in PD impairs resistance to distracters, which results in attention disorders.

Silva Lopes et al. (2014)	HC = 33 PD = 44	PD = 7±6	HC = 60 PD = 64	Two-tone auditory oddball task. Frequent task (80%) and infrequent task (20%) of tones. Patients were assessed using the MMSE and were eligible if they had a diagnosis of idiopathic PD.	A multivariate analysis was performed to verify which variables could influence P300 latencies. The data demonstrated that PD subjects over 65 years old have prolonged P300 latencies was compared to normal controls and this prolongation is more emphasized in individuals in advanced stages of the disease.
Bocquillon et al. (2015)	HC= 15 PD= 15	PD= 4.8	HC= 59.1 PD= 59.2	Three-stimuli visual oddball task (stimuli, target, distractor). 2 different task types: (a circle task with squares as distracters) (square task with circles as distracters) with 360 stimuli each. Patients were classified using the DSM-IV criteria and PD dementia criteria.	In comparison to HCs, only the distractor-elicited P300 component decreased. The oddball-elicited P300 component was poor in PD patients in comparison to HCs. The two groups also did not differ significantly in reaction times.
Kaufman et al. (2016)	HC = 12 PD = 14	HC = 61.7 PD = 63.3	PD = 10.1	Three-stimulus visual oddball task. Distractor stimuli was either a large grey square or a multi-coloured grey square which appeared infrequently (15%). Patients were classified using the MMSE and needed a score of >26 to be included. Cognitive tests were performed while participants were on medication.	P3 activity had a broad distribution for healthy controls, while PD patients showed marked reductions in centro-frontal P3 amplitudes for distracters and targets presented during the colour distracter block. First, PD patients exhibited reduced distracter-related ERPs over centro-frontal electrode sites, indicating disruptions in attentional orienting toward novelty. Second, executive functioning in PD independently correlated with distracter related P3 potentials; however, apathy remained a significant predictor even when accounting for executive function.

Green et al. (1996)	n= 10 per group (PD-younger, PD-older, HC-older, and HC-younger)	All PD patients had been diagnosed within the 4 years prior to the study.	HC (younger)= 43.3 HC (older)= 64.5 PD (younger)= 43.7 PD (older)= 64.4	Two-tone auditory oddball task (rare 'target' tones and frequent 'non-target' tones). Event probabilities were rare 'target' tones (14%) and frequent 'non-target' tones (86%). PD was classified by neurologists.	Both groups of PD patients showed larger P300 amplitude compared to HCs. There was significant latency variation for the PD groups, although the topographic change was less consistent.
Maidan et al. (2019)	YA = 11 OA = 10 PD-N = 10	YA = NA OA = NA PD-N = 2.9	YA = 32.3 OA = 67.1 PD-N = 60.5	Two-stimulus auditory oddball task. Standard stimulus was 600 Hz and the target stimulus were 1200 Hz. Interstimulus interval between 2.8-3.2 s. Target stimulus was 25% of total tones (10/40). Participants were required to count the target tones quietly and either walk or stand on a treadmill. Classified using the MoCA.	P300 latency became longer during walking in all groups. During walking, OA and PD-N participants showed prolonged latency compared to YA. PD-N patients demonstrated reduced P300 amplitude during walking compared to standing. Overall, better motor and cognitive performance correlated with shorter P300 latency for all groups. P300 was not specified, however we may assume from the task type that they are referring to P3b as there is no distractor stimuli in this 2-stimulus auditory task.
Hunerli et al. (2019)	HC = 23 PD-N = 23 PD-MCI = 21	PD-N = 4.09 PD-MCI = 4.81	HC = 66.7 PD-N = 67.3 PD-MCI = 69.8	Two-stimulus visual oddball task. Probability of target was 40/120. ISI was between 3 and 7s. Participants were asked to count target stimuli. For PD-MCI diagnosis, impaired performance in at least two neuropsychological tests was required (i.e., either two tests assessing one cognitive domain or at least two tests assessing different cognitive domains).	PD-N participants demonstrated reduced P300 amplitudes compared to HC. PD-MCI participants had lower P300 amplitudes than both PD-N and HC and reduced volumes of putamen. Findings support that P300 amplitude may be a useful marker for the detection of pre-clinical changes before the appearance of cognitive and structural deterioration in PD.

Toda et al. (1993)	HC= 15 PD= 35 (PD-N= 26, PDD= 9)	NA	HC= 65.8 PD-N= 67.2 PDD= 67.9	Three-stimuli visual oddball task (rare target, rare non-target, and frequent non-target). Event probabilities: rare target (19%), rare non-target (19%) and frequent non-target (62%). PD was classified using MMSE scores and DSM III.	No significant differences in P300 amplitude or latency between PD-N and HC, although PD-N had longer RT. Patients with PDD showed longer P300 latency and RT, compared to HC. This suggests that response selection and execution are impaired in patients with PD-N.
Tanaka et al. (2000)	HC= 11 PD = 29 (IN= 15, MD= 7, SD = 7)	PD = 6.4 (IN= 5.6 MD= 6.7 SD = 7.7)	HC= 68.2 PD = 65.7 (IN= 64.1 MD= 70.4 SD = 64.1)	Two-tone auditory oddball task (rare 'target' tones and frequent 'nontarget' tones). PD patients were diagnosed based on the MMSE.	PD-N patients were reported as displaying an increased amplitude of P300 elicited in response to target stimuli (between 250-400 ms) compared to HC and PDD patients.
Seer et al. (2016)	Review article of P3 measures using the oddball task in those with PD.			Focusing on the P3a and P3b components of the ERPs in PD. Studies included in the review had participants complete a two or three-stimulus visual or auditory oddball task during an EEG recording.	There is reliable evidence for prolongation of P3b latency in demented, but not in non-demented PD patients, suggesting that a decrease in the speed of stimulus evaluation occurs in PDD, but not in non-demented PD. Overall, the P3a amplitude findings in non-demented PD must be considered equivocal, and it appears that differences between PD patients and controls are not very large. Further studies are required to clarify whether ERPs can make useful contributions to the routine assessment of cognitive symptoms.

Abbreviations: EEG = Electroencephalogram; HC = Healthy controls; IN = Intellectually normal; ISI = Interstimulus intervals; MD = Moderately demented; NA = Not available; PD = Parkinson's disease; PDD = Parkinson's disease with dementia; PD-N = non-demented Parkinson's disease; PD-MCI = Parkinson's disease with Mild Cognitive Impairment; RT = Reaction time; SD = Severely Demented; YA = Young Adults; OA = Older Adults

3.8 Summary

EEG is a well-established, low cost technique that has previously been used to assess a range of neurological conditions including AD and PD. It is non-invasive and as a result can be used on a variety of patients and conditions. EEG has been frequently used in the PD literature to assess cognitive changes and differences between participant groups. Due to EEG being able to acquire data that has high temporal resolution, it provides an advantage over other imaging techniques, and does not exacerbate anxiety or claustrophobia. As PD is a neurodegenerative disease that currently has no cure, treatments for symptoms, especially cognitive decline, are at the foremost of management options.

The resting-state literature has a major focus on the spectral power of different frequency bands, especially the theta and alpha band in PD. There is limited research on IAF, and only a few studies have looked at the IAF in PD. Three studies have looked at IAF differences in PD and reported that IAF is decreased in cognitively impaired PD patients. Spectral power literature has shown general trends that show alpha spectral power is reduced in cognitively impaired groups and theta spectra power is increased. Alongside spectral power, functional connectivity has also been investigated in PD. General trends indicate that functional connectivity is reduced in the alpha band in patients who are cognitively impaired. Studies using the oddball task in PD have specifically focused on the P300 component. These studies have found conflicting results regarding the amplitude and latency of the P300 component when looking at a target and distractor stimulus. Several studies have reported that, when compared to healthy controls, PD participants had a lower amplitude and longer latency, whereas other studies have reported no amplitude or latency changes. Previous resting-state and oddball task literature have classified their participants using markedly variable criteria for PD-MCI. As these criteria are not consistent across studies, this highlights potential issues with previous work regarding classification of cognitive ability. However, with the addition of Myall et al. (2020) criteria, this aims to build on the previous classification criteria by using cognitive tests that have been shown to identify high risk of conversion to dementia in PD.

Due to the significant impact cognitive decline has on quality of life in PD, identifying EEG markers that can characterise cognition would be beneficial in the future. Therefore, in this project we investigated EEG using spontaneous resting wakefulness and a three-stimulus visual oddball task to investigate cognitive decline in PD patients who had their cognition classified using the Myall et al. (2020) criteria to determine markers that can be used to characterise cognition.

3.9 Study Aims and Objectives

This thesis investigated EEG markers of cognitive status in Parkinson's disease (PD) by way of a three-stimulus visual-oddball ERP task and spontaneous EEG during resting wakefulness. PD participants were classified into three cognitive groups and compared with healthy controls (HC): those with PD who have relatively normal cognition (PD-N); PD patients meeting criteria for PD-MCI; and PD patients meeting criteria for dementia (PDD). The non-dementing PD patients were classified using a variant of MDS PD-MCI criteria that had been devised to improve the identification of patients with high risk of progression to PDD, developed by Myall et al. (2020). The EEG session was conducted to (1) determine ERP group differences between an easy and hard three-stimulus visual oddball task in a subset of PD-N and HC groups; (2) examine the easy oddball task in the four groups; (3) determine individual alpha frequency (IAF) and relative spectral power group differences during resting wakefulness; and (4) EEG functional connectivity during resting wakefulness.

Chapter 4: Task difficulty in a visual oddball task

4.1 Introduction

Cognitive impairment is a prevalent symptom in PD, with many people experiencing cognitive decline over the course of their disease (Aarsland et al.; J. Goldman & Litvan, 2011; Nijkrake et al., 2007; Weintraub et al., 2018). As approximately 80% of those diagnosed with PD progress to dementia (PDD) within 20 years of the disease, establishing markers to determine future cognitive decline is important (Hindle et al., 2013). As mentioned in Chapter 3, task-based EEG, especially oddball tasks, have been used to investigate neurological conditions and cognitive decline (Hunerli et al., 2019; Seer et al., 2016; Toda et al., 1993). Previously, task difficulty has only been investigated between HC groups, most commonly using a two-stimulus visual oddball task (Hagen, Gatherwright, Lopez, & Polich, 2006; Kim, Kim, Yoon, & Jung, 2008; Polich & Comerchero, 2003). Although these oddball tasks have been used in the HC literature, comparing differences between oddball tasks of varying difficulty in PD is novel.

As mentioned, ERPs are a substantial fluctuation in voltage due to stimulus-evoked neural activity (Picton et al., 2000). A three-stimulus visual oddball task has been used to investigate ERP differences in PD (Seer et al., 2016). The P300 is the most common wave measured in an oddball task and is a positive component of an ERP which peaks at approximately 300 ms, although this can vary between 200-900 ms (Linden, 2005). The subcomponents of the P300, P3a and P3b, are associated with the infrequent distractor and infrequent target stimuli, respectively (Polich, 2007). The P3a distractor amplitude is associated with attentional processes and executive function in PD and the P3b target latency has been associated with general cognitive impairment (Adamski, Adler, Opwis, & Penner, 2016; Disbrow et al., 2014; Seer et al., 2016).

Previous three-stimulus visual oddball task literature has reported mixed findings for the P3a and P3b amplitude and latency. Seer et al. (2016) conducted a review study that summarised P3a and P3b findings in the literature. They reported that overall P3b latency is prolonged after a target stimuli has been presented for a non-demented PD group compared to the HC group (Bocquillon et al., 2012; F. Li et al., 2015; Toda

et al., 1993). Whereas all studies except one reported no difference in P3a latency between non-dementing PDs and HC groups (Bocquillon et al., 2012; Gaudreault et al., 2013; M. Li et al., 2005; Wang et al., 2000). The previous literature focuses on non-dementing PDs which is often not clear whether this includes PD-N participants, making it uncertain what the effects would be in PD-N participants. The P3a and P3b ERPs can also be measured using oddball tasks of varying difficulty to assess differences between groups and have been investigated in healthy controls (HCs) (Gajewski & Falkenstein, 2013; Hagen et al., 2006; Kim et al., 2008).

There is little research on P300 event related potentials (ERPs) in PDD, and to our knowledge no literature that has looked at task difficulty in PD. This addition to the PD literature would help to clarify previous three-stimulus visual oddball ERP studies who have not examined task difficulty in their studies. This would be beneficial to determine whether task difficulty explains some of the different findings in the oddball literature for PD. In healthy controls, prior cross-sectional research reports increasing a task difficulty leads to prolonged P300 latency and reduced amplitude (Gajewski & Falkenstein, 2013; Hagen et al., 2006; Kim et al., 2008). These studies used oddball tasks, which included the three-stimulus visual oddball and two-stimulus visual oddball tasks. The most common oddball task used was the two-stimulus visual oddball task, where there was a standard stimulus and an infrequent stimulus that required a response (Kim et al., 2008; Polich & Comerchero, 2003).

The aim of the present study was to investigate differences in ERPs for different task difficulties, and between groups within a task, in a HC and a PD group who have been classified as PD-N (i.e. do not meet criteria for PD-MCI). Using PD-N participants in this study would provide an understanding to the effect on ERPs and task difficulty when cognition is relatively intact and whether effects can be more closely tied to decreasing cortico-striatal pathways. The study used two variations of a three-stimulus visual oddball task, classified as ‘easy’ and ‘hard’, in a cross-sectional design, and classified PD-N participants on the basis of neuropsychological performance using the NZBRI criteria. To our knowledge, the effect of task difficulty has not been explored using a three-stimulus visual-oddball task in PD. This study extends prior HC literature and adds an original aspect as current literature has not investigated oddball task

difficulty in PD-N participants compared with HCs. Investigating these differences in participants classified as PD-N will outline the effect of task difficulty on ERPs using a three-stimulus visual oddball task.

4.2 Method

4.2.1 Participants

PD-N status was established based on not meeting impaired performance on any two of ten neuropsychological measures. This criterion for classifying cognition was outlined in Section 2.5. Table 4.1 lists the ten neuropsychological test variables used. HC participants also completed comprehensive neuropsychological testing, to ensure that they were not cognitively impaired.

A convenience sample of 63 participants, comprising 39 PD and 22 HC, was recruited between 2018-2020 from the New Zealand Brain Research Institute (NZBRI) Longitudinal Progression study. Participants were excluded if they had any other neurological conditions, had previous deep brain stimulation, a metal plate in the head region, or previous history of major psychiatric illness, or drug or alcohol abuse. Non-demented participants received a comprehensive battery of neuropsychological tests, which was used to identify cognitive ability of participants. Six participants were identified from these neuropsychological tests as being PD-MCI and were excluded. Two other participants did not complete the neuropsychological assessments and were excluded. The remainder of participants were classified into PD-N (N = 33), and HC (N = 22). PD-N participants received at least 10 neuropsychological tests, but one participant had 9 test scores. This participant was included in the data analysis. Most HC participants (N = 20) also received the same battery of neuropsychological tests. All participants had normal or corrected-to-normal vision. PD participants continued their medication regime during the current study. The Northern B Health and Disabilities Ethics Committee approved the study including consent prior to the EEG session. Participants were reimbursed for their travel costs.

EEG data were recorded within a six-month window of the comprehensive neuropsychological testing for non-demented patients; 9 participants did not meet this

criterion and were excluded. The percentage number of at least 70% correct target trials not being met resulted in a further 4 participants being excluded. There was a final sample size of 38 participants across the two groups (Figure 4.1). All participants had normal or corrected-to-normal vision and continued their usual medication regime during all assessments. All PD participants were tested during "on" periods of medication and assessments were re-scheduled if the participant reported that they were experiencing an "off" medication episode. The flow of participants included for this study is summarized in Figure 4.1.

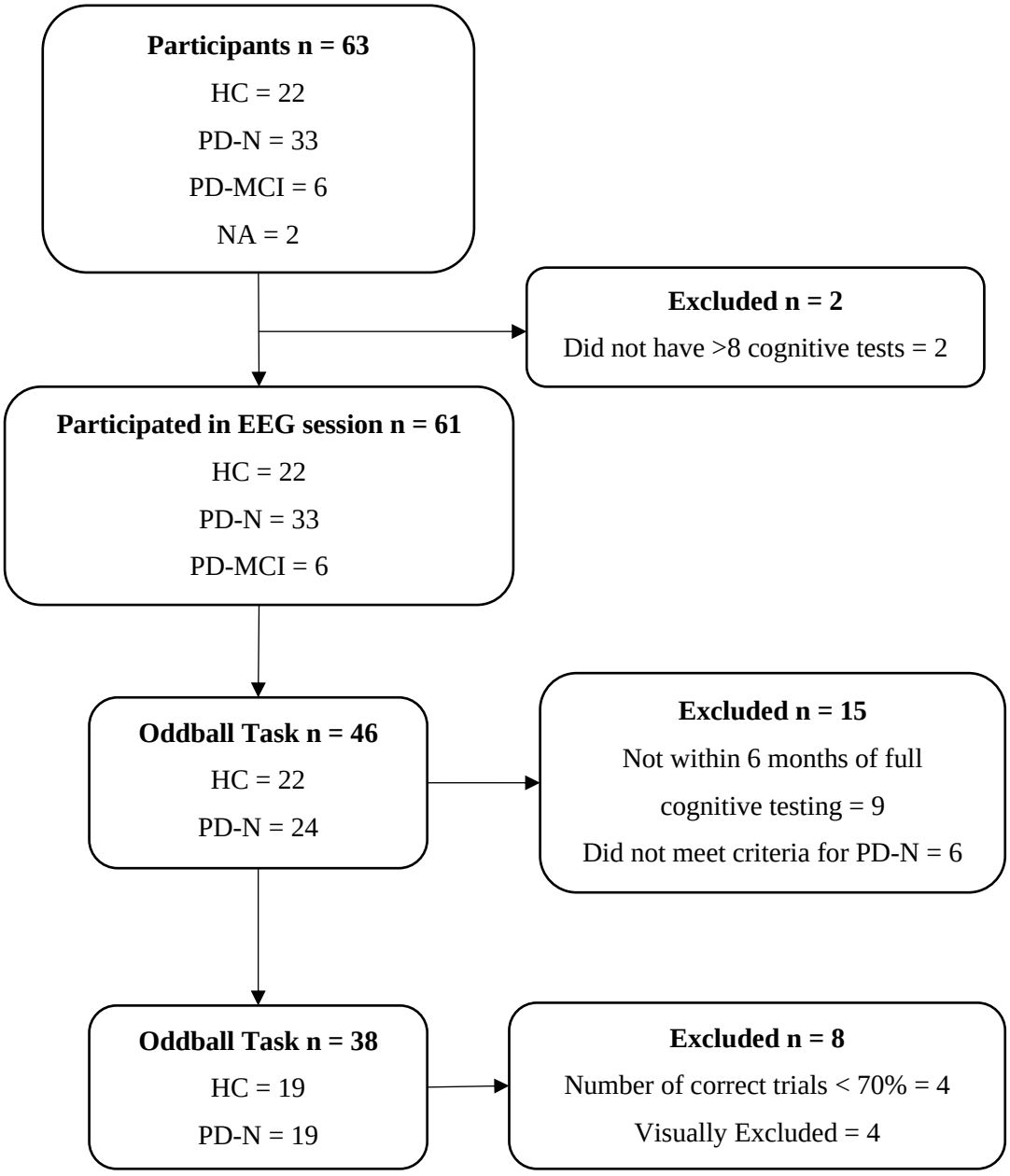

Figure 4.1 STARD chart for participants – easy versus harder oddball task.

4.2.2 Task and EEG Recordings

EEG was collected within a six-month window of neuropsychological testing for PD-N participants. Participants completed the EEG session in a quiet testing room at the NZBRI. EEG data were acquired using a 64-electrode Neuroscan Compumedics Quik-cap while the participant sat comfortably but as still as feasible, while instructed to complete both an 'easy' and 'hard' version of a three-stimulus visual oddball task for approximately 25 min each. EEG recordings were obtained directly after a 10-min eyes-closed resting-state condition.

Both the 'easy' and 'hard' version of the three-stimulus visual oddball task required the participant to make a manual response to an infrequent target stimulus (8%) and refrain from responding to a frequent (84%) standard stimulus and an infrequent (8%) distractor. The oddball task comprised of a circle subtask with square distracters and a counterbalanced version in which the circle was the distractor, each with 250 stimuli (Figure 4.2). The stimuli were all solid blue shapes and were displayed against a light grey background. In the easier version, the target stimulus was 60% of the area of the standard and distractor stimuli, and duration of stimuli was 300 ms; in the harder version, the target stimulus was 82% of the area of the non-target stimuli and was 80 ms stimulus duration. The interstimulus interval range for each task difficulty level was 1800–2200 ms. Participants were instructed to respond to the appearance of the target stimulus within 2000 ms by pressing a button with their dominant hand and ignore (do not press) the button for both the distractor and standard stimuli. The button's location on the Chronos Box™ was arranged to suit the participant's dominant handedness.

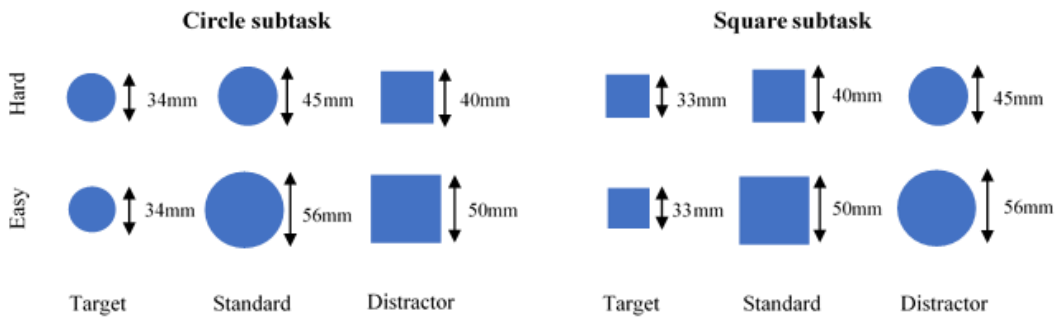

Figure 4.2 Visual stimuli used in the easy and hard version of the oddball task for the circle target and square target subtasks.

Practice trials were conducted before each task, but without the distractor stimuli, in which there were 45 stimuli for each subtask with a probability of 0.33 for targets and 0.66 for standard shapes. Participants repeated the practice procedure up to three times if they performed below 70% accuracy (both target detection and the standard shape). The reaction time, omission rate, and the stimulus commission rates were recorded. The omission rate was the number of misses divided by the total number of targets x 100. The overall distracter commission rate was the number of false alarms after the appearance of a distracter divided by the total number of distractors x 100. The commission rate was the number of false alarms divided by the total number of non-target stimuli (distracter and standard stimuli) x 100. Four participants were unable to complete at least 70% of trials and were therefore excluded from the analyses.

E-Prime (Professional Suite; run-time version 2.0.10.353; Psychological Software Tools, Inc.) was used to run the three-stimulus oddball task. The participant sat approximately 60 cm in front of a 22-inch computer screen. The researcher used a second screen directly behind the participant to control the experiment and thus not disturb them. The experiment was conducted in an evenly lit room, during either a morning or afternoon session. The lights remained on throughout the entire session.

4.2.3 EEG Analysis

EEG data were analysed offline in EEGLAB (Delorme & Makeig, 2004; Delorme et al., 2011). EEG was band-pass filtered from 0.1 Hz to 75 Hz and downsampled to 250 Hz. Prep pipeline was used to minimize line noise (i.e., 50 Hz), identify bad electrodes, and re-reference to a robust average of all electrodes (Bigdely-Shamlo, Mullen, Kothe, Su, & Robbins, 2015). Artefact subspace reconstruction (ASR) was used to remove large artefacts (Chang, Hsu, Pion-Tonachini, & Jung, 2020; Mullen et al., 2015). Infomax independent component analysis (ICA) was applied to identify and remove stereotypical artefacts such as eye blinks (Delorme, Sejnowski, & Makeig, 2007). Artefactual components were identified using ICLabel and FASTER plugins of EEGLAB (Nolan, Whelan, & Reilly, 2010; Pion-Tonachini, Kreutz-Delgado, & Makeig, 2019). Furthermore, components with a corresponding current dipole outside the brain were removed. EEG data were then epoched from -200 ms to 1000 ms with respect to the

onset of trials, linear trends were removed, and pre-stimulus data were used for baseline correction. Epochs were inspected and noisy ones were rejected. Finally, remaining epochs of each condition were averaged to form ERPs.

A participant was excluded from analysis if more than 10 electrodes were identified as "noisy" (had an impedance of greater than 10 kΩ). A further four participants were visually excluded from the analysis if there was no visible P300. Latency of the P300 was taken between 200-900 ms. ERPs for the amplitude and latency were both assessed globally over the whole scalp and over electrode-defined regions for each version of the oddball task (easy or hard). The regions used in this study were defined as Anterior, Central and Posterior regions (Figure 4.3). ERP waveforms were averaged across electrodes for each analysis. Grand averages and reaction times were also assessed.

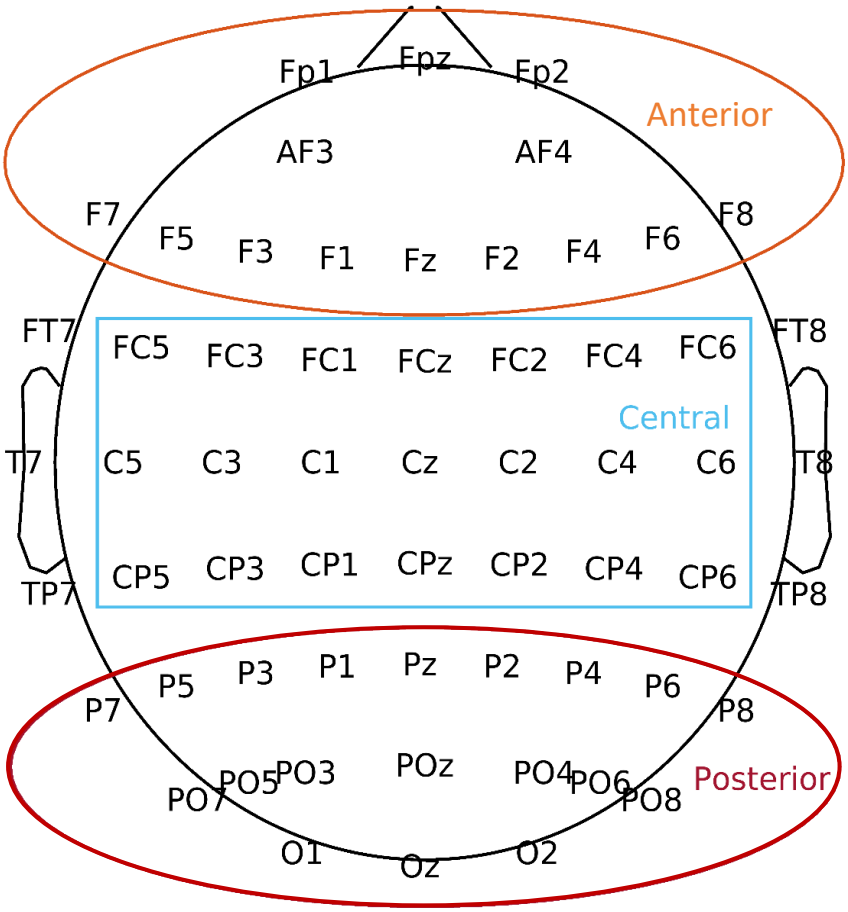

Figure 4.3 Three regions used to classify regional electrode clusters.

4.2.4 Statistical Analysis

Statistical analyses were conducted in R version 3.6.3. Median reaction was compared across the two groups and two task difficulty versions using a two-way ANCOVA with age and sex as covariates. As neither age nor sex were statistically significant for reaction time (all $t < 0.41$, all $p > 0.69$), an unadjusted two-way ANOVA was used to show mean values for the reaction time.

The amplitude and latency of the P300 component corresponding to each stimulus were analysed separately, resulting in 6 (3 stimuli × amplitude and 3 stimuli × latency) analyses. For each analysis, a three-way repeated-measure ANOVA was used with group as the between-subject factor, and region and task difficulty as the repeated measure factor. Significant group main effect or significant interactions were further explored by post-hoc analysis. Tukey post-hoc comparisons determined pairwise differences between groups and adjusted $p < 0.05$ was considered statistically significant. All confidence intervals are ±95%.

4.3 Results

4.3.1 Participant Demographics and Group Characteristics

The demographics of the PD and HC groups are described in Table 4.1. Global Z scores are shown, which are based on the average z-scores both across the "ten sensitive cognitive measures" used to define the PD-N group and, for comparison, the 21 neuropsychological tests used previously at the NZBRI to summarise cognition in patients with PD-MCI. The Global Z score for the 21 tests were calculated by averaging scores within each domain before computing an average of those domain scores. Although the neuropsychological test scores for the PD-N group were in the normal range, the HC group performed better on all tests except the Map Search 1 min and the Rey Intermediate Recall. There were no statistically significant differences between groups for sex, education, MoCA, ADL, and WTAR measures. There were significant differences between groups for age. However, when age was used as a covariate in the analysis, it did not have a significant effect.

Table 4.1 Demographic, neuropsychological and neuropsychiatric measures for all participants with exclusions (mean ± SD).

Measures	HC	PD-N	p < 0.05
N	19	19	
Male/Female	11/8	8/11	
Mean Age ± SD (years)	75.5±8.4	66.1±6.2	*
Symptom Duration ± SD (years)	-	8.5±4.5	
LEDD	-	1165.2±1848.7	
Hoehn & Yahr Stage	-	2.0±0.4	
UPDRS III	-	22.6±8.7	
Education (years)	13.9±2.9	14.1±2.4	
Reisberg ADL	0.3±0.4	0.3±0.3	
MoCA	26.6±2.3	27.6±2	
Global Z 21 tests	0.87±0.43	0.51±0.37	
Global Z 10 tests	0.74±0.37	0.35±0.36	
Premorbid IQ (WTAR)	113±7.66	112.95±7.21	
NPI	-	6.57±4.5	
Executive Function			
Stroop Interference	**0.88±0.65**	**0.65±0.83**	
Trails B	**0.76±0.73**	**0.62±0.56**	
Action (verb) Fluency	-0.07±1.18	-0.1±1.27	
Letter Fluency	1.09±1.4	1.47±1.13	
Category Fluency	1.75±1.05	1.39±0.77	
Category Switching	0.84±1.05	0.74±0.77	
Attention			
Digit Ordering	**-0.10±1.49**	**-0.79±0.77**	
Map Search 1min	**0.37±0.59**	**-0.23±0.92**	*****
Stroop Word Reading	0.39±0.58	0.54±0.54	
Stroop Colour Naming	0.35±0.71	0.25±0.68	
Digits Forward & Back	1.07±1.13	0.86±1.17	
Trails A	0.91±0.56	0.63±0.6	
Episodic Memory			
CVLT II Total Immediate Recall	**1.79±0.99**	**1.26±1.30**	
Rey Immediate Recall	**0.81±1.49**	**1.12±1.12**	
CVLT II Long Delay	1.11±1.05	0.37±0.86	*
Visuoperceptual			
Rey Copy	**-0.17±0.87**	**-0.06±0.88**	
Judgement of Line	**0.16±0.91**	**0.35±0.59**	
VOSP Fragmented Letters	0.67±0.64	0.47±0.61	
Language			
Mattis DRS-2: Similarities	**0.17±0.46**	**0.17±0.37**	
ADAS-Cog: Language	**-0.04±0.62**	**0.05±0.58**	

All pairwise comparisons are not significantly different (except age, map search, CVLT II long delay).
Bolded text indicates the ten neuropsychological tests used in Myall et al. (2020) for cognition.
Cognitive measures are z-scores. Abbreviations: ADAS = Alzheimer's Disease Assessment Scale; ADL = Activities of Daily Living; CVLT = California Verbal Learning Test; DRS = Dementia Rating Scale; HC = Healthy Control; MoCA = Montreal Cognitive Assessment; NA = Not Applicable; PD-N = Participants with PD who have relatively normal cognition (i.e. do not meet the criteria for PD-MCI); SD = Standard Deviation; UPDRS = Unified Parkinson's Disease Rating Scale; VOSP = Visuospatial Object and Space Perception; WTAR = Wechsler Test of Adult Reading

4.3.2 Reaction Time

For each participant, reaction times were estimated as the median of the corresponding reaction times for all correct trials for the target, distractor and standard stimuli, and difficulty, as shown in Figure 4.4. Reaction time was longer in the PD-N group compared to the HC group (Means = 535 ms vs 486 ms, F(1,35) = 4.64, p = 0.04). Similarly, reaction time (i.e., collapsed across groups) was higher in the hard task compared to the easy task (Means = 524 ms vs 496 ms, F(1, 36) = 6.64, p = 0.01). However, there was no significant Group × Difficulty interaction (F(1,35) = 0.20, p = 0.66).

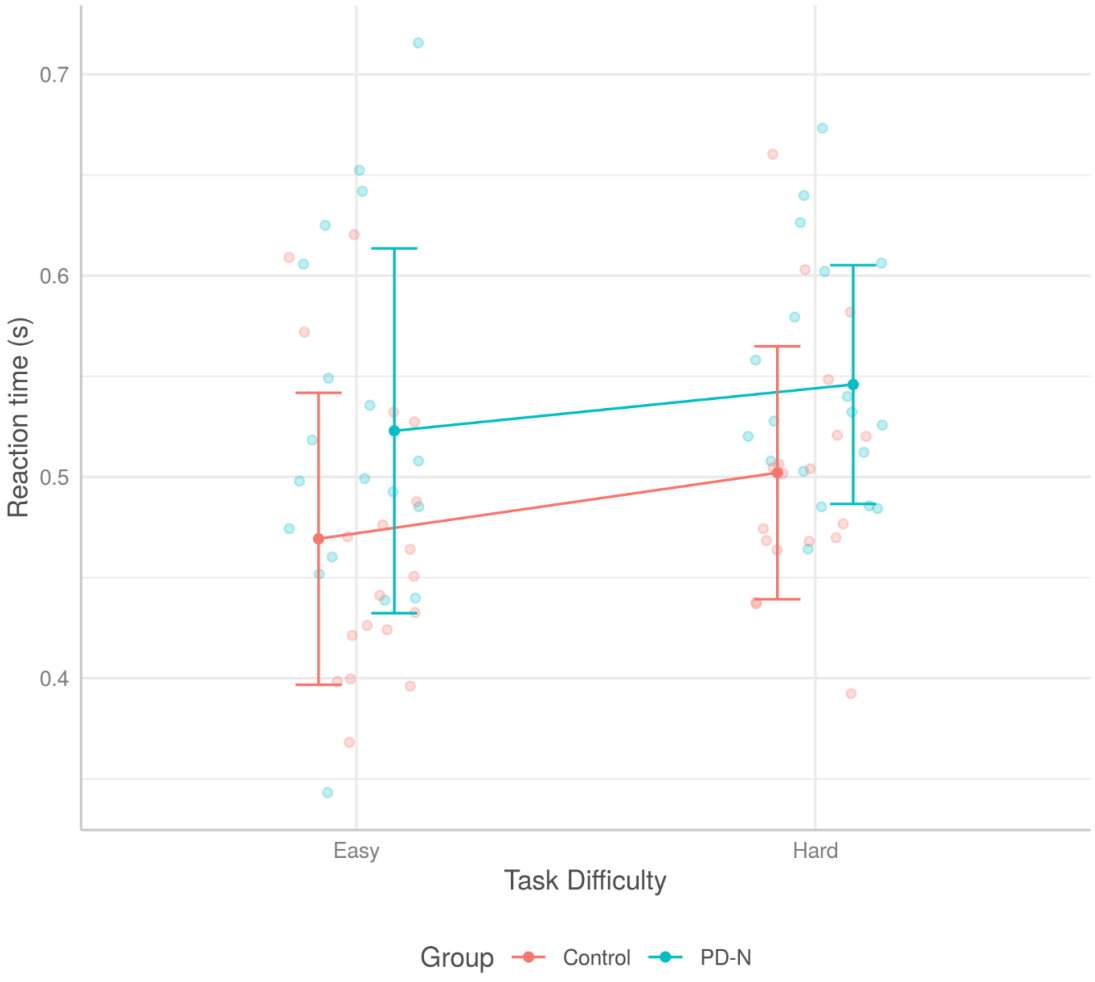

Figure 4.4 Reaction time ± SD for the two groups with corresponding individual values.

4.3.3 Grand Average ERP Waveforms

Grand average ERP waveforms are shown in Figure 4.5. To further analyse ERP waveforms, the amplitude and latency of the P300 component were extracted for each stimulus and difficulty. This was done by finding the corresponding amplitude and latency of the ERP peak between 250 and 900 ms.

The subtraction wave for the target-minus-standard, distractor-minus-standard and target-minus-distractor subtraction waves were calculated for both the easy and hard task, which allowed both P3a and P3b to be localized in both time and space (Figure 4.6). The subtraction waves calculated minimized the baseline drift for both the easy and hard task. Furthermore, for the easy task, the distractor-minus-standard wave minimised the amplitude of the P3a wave and was smaller than the target-minus-standard and target-minus-distractor.

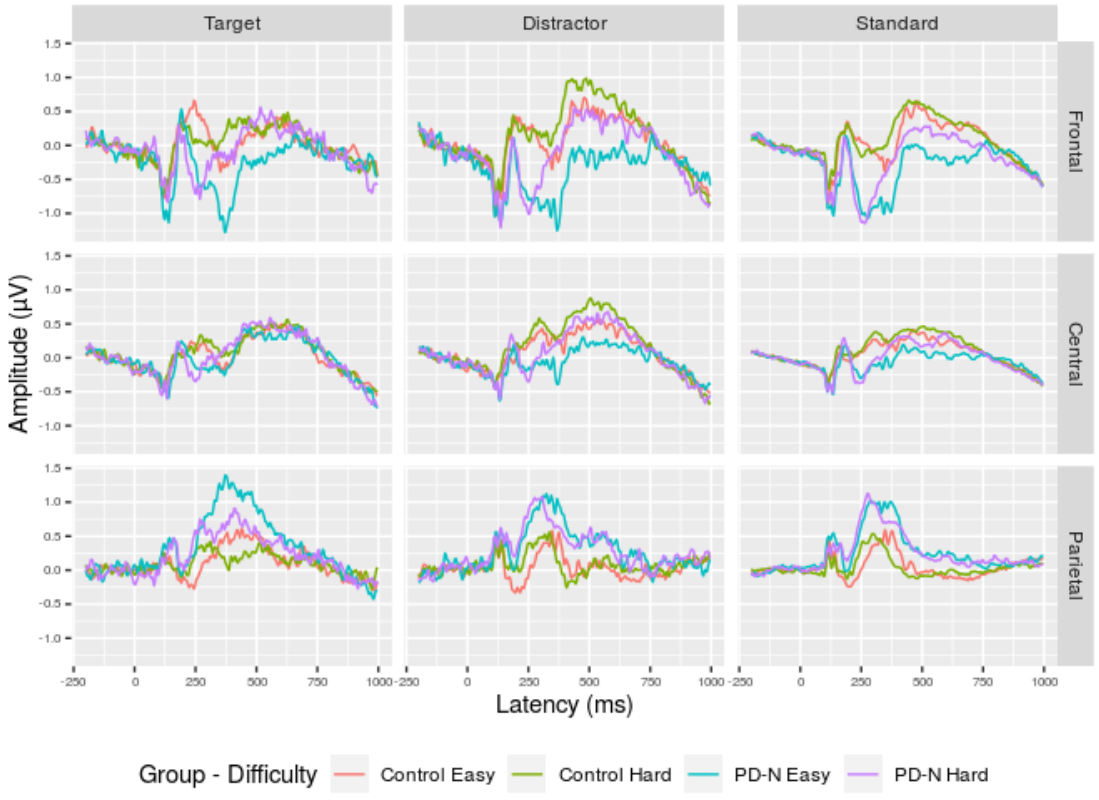

Figure 4.5 Grand averages for three stimuli for the two groups, across the three electrode regions. Control = Healthy controls; PD-N = PD with relatively normal cognition.

Figure 4.6 Subtraction waves for the HC and PD-N group, for the easy and hard task, respectively across the three electrode regions.

4.3.4 P300 Latency

P300 latencies across groups and conditions are shown in Figure 4.7. The findings remained the same when age and sex were included as covariates. Differences between groups were particularly evident in the anterior region. Latency, collapsed across task difficulties and groups, showed a pattern of gradual prolonged latency from the anterior to the posterior region (all $F(2, 180) > 8.5$, all $p < 0.001$). There was no Group × Difficulty interaction for all stimuli (all $F(2,180) < 1.86$, $p > 0.18$). There was also no significant Group × Region × Difficulty interaction for all stimuli (all $F(2,180) > 0.36$, $p > 0.31$). Significant Group × Region interactions were found for all three stimuli and

followed up with simple main effects analyses and post-hoc pairwise comparisons in the following section.

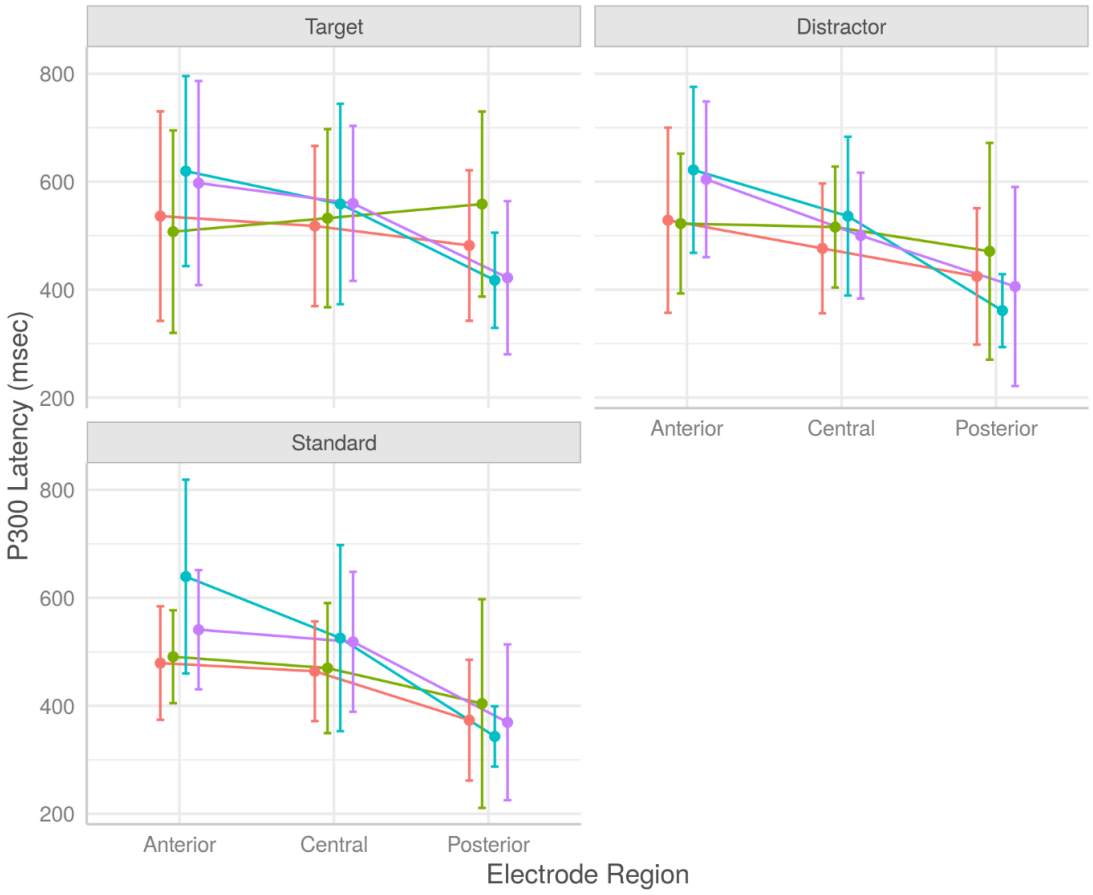

Figure 4.7 Mean latency ± SD for three stimuli in the four groups, across the three electrode regions, for the easy and hard task.

For the target stimuli, there was a significant Group × Region interaction ($F(2, 180) = 8.02$, $p < 0.001$). This interaction was followed up with a significant main effect for Region ($F(2, 180) = 8.50$, $p < 0.001$). The PD-N group had longer latencies in the anterior region, and this decreased to the central and posterior regions. The HCs did not show any difference in latency across regions. The PD-N group for both tasks was higher than the HC group in the anterior region, whereas there were no differences between groups in the central region. In the posterior region there was a significant difference between the PD-N and HC group for the hard task ($d = 0.86$, CI = 0.09, 1.63, $p = 0.03$). There was no significant main effect of Group ($F(1,35) = 0.19$, $p = 0.66$) or Difficulty ($F(1, 180) = 0.15$, $p = 0.70$).

For the distractor stimuli, there was a significant Group × Region interaction ($F(2, 180) = 6.63$, $p < 0.001$). There was a reduction in latency across anterior to central and then to the posterior electrode regions, which was supported by a significant main effect for Region ($F(2, 180) = 27.29$, $p < 0.001$). The PD-N group had longer latencies in the anterior region, and this decreased across to the central and posterior regions although there were no significant pairwise comparisons. The HC did not show any difference in latency across regions. The PD-N group for both tasks was higher than the HC group in the anterior region, but there were no differences between groups in the central and posterior region. There was no significant main effect of Group ($F(1, 35) = 0.30$, $p = 0.59$) or Difficulty ($F(1, 180) = 0.48$, $p = 0.49$).

For the standard stimuli, there was also no significant Group × Region × Difficulty interaction ($F(2, 180) = 1.18$, $p = 0.31$). There was a reduction in latency across anterior to central and then to the posterior electrode regions, which was supported by a significant main effect for Region ($F(2, 180) = 40.05$, $p <0.001$). The PD-N group had longer latencies in the anterior region, and this decreased to the central and posterior regions. The HC group had stable latencies between the anterior to central region, although this decreased from the central to posterior region. There was a significant difference between the HC and PD-N group for the easy task in the anterior region ($d = -1.16$, CI = -1.95, -0.37, $p = 0.003$). There was also a significant difference between the PD-N group for the easy and hard task in the anterior region ($d = 0.83$, CI = 0.17, 1.50,

p = 0.01). There was no significant main effect of Group (F(1, 35) = 0.44 , p = 0.51) or Difficulty (F(1, 180) = 0.11, p = 0.74).

4.3.5 P300 Amplitude

P300 amplitudes across groups and conditions are shown in Figure 4.8. The findings remained the same when age and sex were included as covariates. Differences between groups were particularly seen in the posterior region. Latency for the target stimuli was increased overall for the target stimuli compared to the standard stimuli. Amplitude, collapsed across task difficulties and groups, showed a pattern of gradual increase from the central to posterior region (all F (2,180) > 7.72, all p < 0.001). There were no Group × Region × Difficulty interactions for any of the stimuli (all F (2,180) < 0.54, all p > 0.58). Significant Group × Region interactions were followed up with simple main effects analyses and post-hoc pairwise comparisons. Regional interactions were found for all three stimuli and followed up with simple main effects analyses and post-hoc pairwise comparisons in the following section.

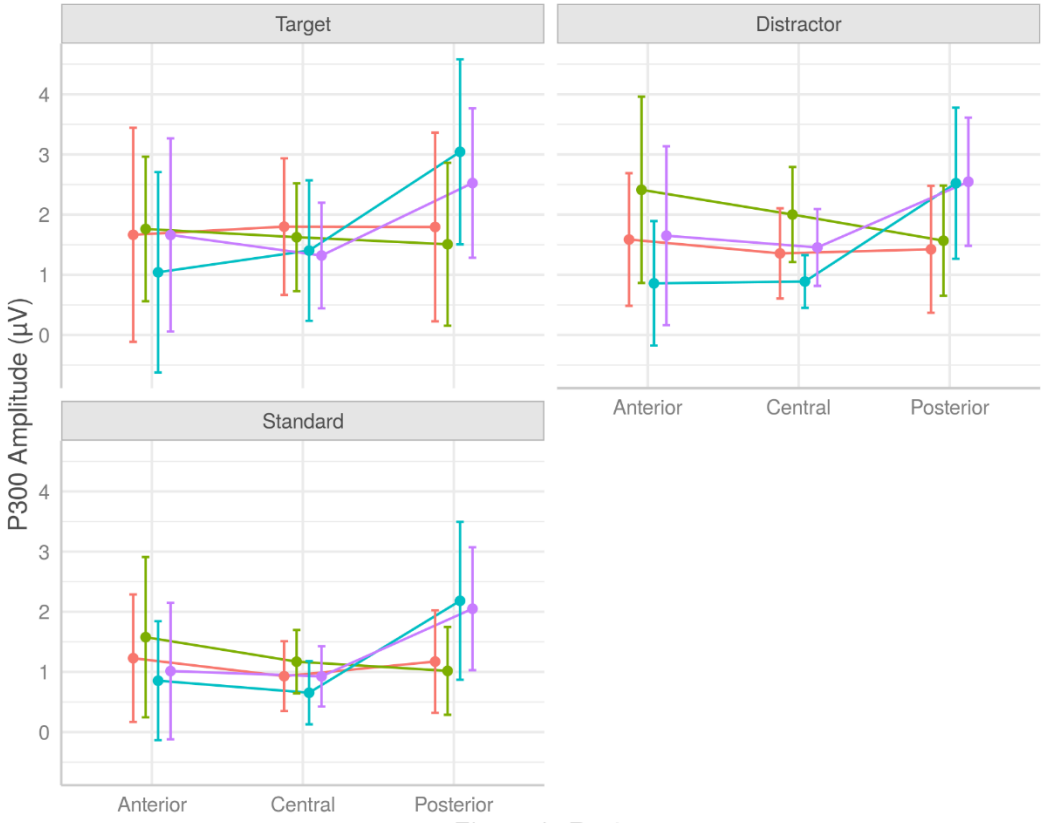

Figure 4.8 Mean amplitude ± SD for three stimuli in the two groups, across the three electrode regions, for the easy and hard task.

For the target stimuli, there was a significant Group × Region interaction ($F(2, 180) = 11.15$, $p < 0.001$). This interaction was followed up with a significant main effect for Region ($F(2, 180) = 9.38$, $p < 0.001$). The PD-N group showed an increase in amplitude for both the easy and hard task across the anterior to posterior electrode regions, this difference was not evident for the HC group. In the posterior region, the PD-N group had the highest amplitude for the easy task. There was a significant difference between the HC and PD-N group for the easy task in the posterior region ($d = -0.91$, CI = -1.78, -0.04, $p = 0.04$). There was no significant main effect of Group ($F(1,35) = 0.06$, $p = 0.80$) or Difficulty ($F(1, 180) = 0.15$, $p = 0.70$).

For the distractor stimuli, there was a significant Group × Region interaction ($F(2, 180) = 20.17$, $p < 0.001$). There was also a significant main effect of Region ($F(2, 180) = 7.72$, $p < 0.001$) and Difficulty ($F(1, 180) = 16.08$, $p < 0.001$), although there was no significant main effect of Group ($F(1, 35) = 0.002$, $p = 0.97$). The PD-N group showed increased amplitude for both the easy and hard task across the central to posterior electrode regions. In the anterior region, the HC group had the highest amplitude for the hard task, although the HC group showed a decrease in amplitude for the hard task across the anterior to the central and to the posterior electrode regions. In the anterior region, there was a difference between the two tasks for the PD-N group ($d = -0.84$, CI = -1.50, -0.18, $p = 0.01$), as well as the HC group ($d = -0.88$, CI = -1.54, -0.22, $p = 0.01$). In the parietal region there was a significant difference between the HC and PD-N group in the easy task ($d = -1.23$, CI = -2.04, -0.42, $p = 0.002$) and hard task ($d = -1.11$, CI = -1.91, -0.30, $p = 0.005$). There was also a significant difference between the easy and hard task in the HC group in the central region ($d = -0.69$, CI = -1.34, -0.03, $p = 0.04$).

For the standard stimuli, there was a significant Group × Region interaction ($F(2, 180) = 18.19$, $p < 0.001$). There was also a significant main effect of Region ($F(2, 180) = 13.45$, $p <0.001$). The PD-N group showed an increase in amplitude for both the easy and hard task across the central to posterior electrode regions, although there was no difference across regions for the HC for either the easy or hard task. In the parietal region there was a significant difference between the HC and PD-N group for the easy task ($d = -1.40$, CI = -2.21, -0.58, $p = 0.001$), as well as the hard task ($d = -1.42$, CI = -

2.24, -0.60, p = 0.001). However, there was no significant main effect of Difficulty ($F(1, 180) = 1.26$, $p = 0.26$), or Group ($F(1, 35) = 1.30$, $p = 0.26$).

4.4 Discussion

The main finding from this study was that the PD-N group displayed higher P3a amplitude in the posterior region across all stimuli for both the easy and hard task, compared to the HC group. The PD-N group also had longer P3b latencies for all three stimuli in the anterior region, compared to the HC group for both tasks. There was a regional effect for the latency and amplitude as the latency decreased on average across the anterior to central to posterior region, whereas the amplitude increased on average from the central to posterior region. Reaction time was shorter for the HC group compared to the PD-N group in both the easy and hard task. It was also prolonged in the hard task compared to the easy task for both groups.

These cross-sectional findings for the study are the first to have investigated task difficulty differences in oddball ERPs in PD. There was no evidence of a classic oddball effect, irrespective of task difficulty, as the P3a and P3b latency and amplitude differences did not differ significantly between groups. Only PD participants with relatively normal cognition were included in the current study (i.e., not meeting criteria for PD-MCI). Anecdotally we looked at task difficulty in PD-MCI participants and these participants were not able to complete the hard task, therefore it was decided to only include HC and PD-N participants in this study. Using PD-N participants in this study helped to provide an understanding of the effect on ERPs and task difficulty when cognition is relatively intact. As previous literature has not investigated this phenomenon in PD, the findings from our study could not be directly compared with previous task-difficulty PD literature (Gajewski & Falkenstein, 2013; Hagen et al., 2006; Kim et al., 2008; Polich & Comerchero, 2003). However, previous literature that has used one oddball task has reported mixed findings for the P3a and P3b amplitude and latency. Seer et al. (2016) found that the overall P3b latency is prolonged for non-demented PDs compared to HCs, whereas the majority of studies reported no difference in P3a latency between non-dementing PDs compared with HCs (Bocquillon et al., 2012; Gaudreault et al., 2013; F. Li et al., 2015; Toda et al., 1993; Wang et al., 2000). Furthermore,

previous literature that has looked at task difficulty in HCs reported increasing task difficulty leads to prolonged P300 latency and reduced amplitude (Gajewski & Falkenstein, 2013; Hagen et al., 2006; Kim et al., 2008). Nevertheless, there were a few significant differences between PD-N participants and the HC group. Thus, it is clear from the findings reported in our study that overall task difficulty had no significant ERP effects.

This study helped to clarify previous ERP literature, to determine if task difficulty may explain some of the different findings in the literature for PD. Currently the literature uses variations of oddball tasks that are both visual and auditory. These variations include different sizes of stimuli used and the number of stimuli presented in any given task. Bocquillon et al. (2012) outlined their version of the three-stimulus visual oddball task which our task is modelled from. Their study used 360 stimuli which were displayed in a semi-random order with an interstimulus interval of 1800 to 2200 ms. Whereas, Kaufman et al. (2016) presented participants with a total of 600 stimuli which were separated into four 150 blocks, and had a 2000 ms interstimulus interval, and Toda et al. (1993) presented between 256 to 320 stimuli that had a 1240 ms interstimulus interval. These variations in stimuli presented in the literature add to the understanding of differences in the oddball task literature in PD. Therefore, the differences in the literature may be attributed to the variations in oddball tasks. For example Kaufman et al. (2016) had the most stimuli in their task and were one of the only studies to report a reduction in P3a amplitude for non-demented PD participants compared to HCs. Even though our study did not report significant task difficulty effects, the difference in reaction time indicates that there was a difference in task that was observed by both participant groups and outlines the potential differences in the previous oddball literature.

This study found no significant task difficulty effect between PD-N and HC groups when using two versions of a three-stimulus visual oddball task. On average the HC participants produced a shorter P3b latency in the anterior region compared to the PD participants for both the easy and hard task for all three stimuli. Furthermore, in the posterior region the PD-N participants had a shorter P3b latency for the target stimuli for the easy and hard task. However, we hypothesised that the PD participants would have a longer P3b latency when compared to the HC. Our study suggests that

individuals with PD-N may be putting more attentional resources into completing the tasks compared with the HC group. These results are contrary to previous three-stimulus visual oddball task literature in PD. This has reported that the P3b latency is prolonged after presentation of a stimulus for non-demented PD participants compared to HCs (Bocquillon et al., 2012; F. Li et al., 2015; Toda et al., 1993). In previous HC literature, when task difficulty increased, the P3b latency was prolonged, and the P3b amplitude was reduced for the target stimulus (Hagen et al., 2006; Kim et al., 2008; Polich & Comerchero, 2003).

The P3a distractor amplitude was higher in the HC group for both the easy and hard task compared to the PD-N group in the anterior and central region. However, in the posterior region, we found that P3a amplitude was increased in the PD-N group compared to the HC group, irrespective of task difficulty. The results from our study do not completely correspond with previous oddball task literature in PD as previous literature has reported a reduction in P3a amplitude in the PD group, compared to the HC group (Kaufman et al., 2016; M. Li et al., 2005; Wang et al., 2000). However, other P3a literature described no significant differences in amplitude between PD and HC groups (Bocquillon et al., 2012; Gaudreault et al., 2013; Tachibana, Toda, & Sugita, 1992).As there is no current task difficulty literature in PD, we are not able to compare findings directly with previous PD literature investigating task difficulty. The PD-N participants in our study have been classified as cognitively un-impaired which may contribute to the non-significant findings and being relatively early on in their disease process could account for the negligible differences between groups. It may also be beneficial to increase the difference in stimulus size and stimulus duration to create a significant difference between the amplitude and latencies for each level of task difficulty.

We did, however, find an association between task difficulty and reaction time. As task difficulty increased, the reaction time to the target stimuli was slightly longer. This difference acts as a manipulation to confirm that the easy versus hard effect has influenced participants. These findings are consistent with previous oddball task research, demonstrating that HC participants are responding to the stimuli faster than the PD participants, regardless of task, and suggests that, overall, PD participants perform

slower than HC (Toda et al., 1993). Other task difficulty research looking at the reaction time for a HC groups has reported that as task difficulty increased, so did reaction time (Hagen et al., 2006; Kim et al., 2008; Polich & Comerchero, 2003). The findings from our study suggest that as task difficulty increases, reaction time increases and PD-N participants take longer to respond to the stimuli; if these reflect longitudinal changes, this may help to identify cognitive decline in PD participants when they are given different task difficulty levels to respond to.

Despite no significant differences between task difficulty, the P300 amplitude displayed an interesting pattern in general as PD-N participants showed elevated amplitude in the posterior region. However, this is a general trend for all stimuli and not specific to an oddball effect. The P3b amplitude was expected to be higher in the posterior region and the P3a was expected to be higher in the frontal and central region, which is not clear in our data. This may indicate relatively more synchronised activity in these groups.

The data contributed to a clearer understanding of the effect of task difficulty, despite the lack of significant findings. There are some strengths to this study, which include the lack of previous literature investigating the effect of task difficulty in PD. As previous task difficulty literature has not investigated group differences in PD, this gives our study an advantage to produce initial research that examines the relationship between task difficulty and HC and PD-N groups. Another strength to the study is the criteria used to classify cognition. Our study used Myall et al. (2020) which identified a selection of ten neuropsychological tests shown to identify high risk of conversion to dementia. We used only participants who were characterised as PD-N and compared them to a HC group to determine any difference between groups as well as between the easy and hard task. This provides a comparison between PD group and the difference between HC and those with PD who are not showing any signs of cognitive decline.

There were several limitations that challenge the utility of this study. Firstly, the difficulty of both tasks may have been relatively similar, despite the difficulty effect found for the reaction time. Nevertheless, future research could add a third task into the session which was a much easier task so comparisons between all three tasks could be

made to determine whether the two initial tasks were different enough from each other. The size of the distractor and standard stimulus could be made even bigger than they currently are for the easy task to ensure that there is a definite difference between the three tasks. Changing the stimulus duration is another way to add or decrease difficulty levels as allowing each shape to be displayed on the screen for longer, gives the participants more time to properly distinguish the stimulus and respond accordingly.

Another limitation is there may have been a potential practice effect due to the instructions of the task. Before the main task was administered for each subtask, there was a practice task which all participants are given and required to achieve at least a 70% correct response rate for the target and at least 70% correct non-response for the standard stimulus. Each practice task had 30 standard stimuli and 15 target stimuli which were given over a two-minute period. This may have affected the current study by masking the observed effects of the P300, especially the P3b amplitude. The practice effect may reduce the amplitude as the target stimulus is not having the desired novel effect due to participants completing the practice task beforehand to ensure they understand the task before them. In order to determine whether this was a contributing factor to the results, implementing a shorter practice task or having the participant do the task once may be an option for future studies.

Aside from the practice task, not having enough trials for each of the stimuli may have also contributed to the results and been a limitation of the study. This is because each participant completed the easy and hard task, each with 50 target stimuli, 50 distractor stimuli, and 500 standard stimuli. When analysed, all epochs with artefacts or which were incorrect responses were rejected. In future studies it may be beneficial to add more trials to each task or have the participant complete the task until they correctly identify a certain number of correct stimuli. This would ensure that there is enough data to analyse and each participant has the same amount of trials to directly compare groups accurately. Finally, increasing the sample size for both groups of participants would increase the statistical power to identify small effect sizes, and expanding the cognitive groups to include those who meet criteria for PD-MCI and especially criteria for PDD would extend the study findings. However, including participants who meet these criteria may prove problematic as PD participants with cognitive impairment

may not be able to perform both tasks, especially the hard task. Nevertheless, adding a third task difficulty level or changing the stimulus duration and size might help to identify any group or task difficulty level effects.

4.5 Conclusion

This study found no evidence of a task difficulty effect between the PD-N and HC group. ERP analysis found that the P3b latency was prolonged for the PD-N group compared to the HC group in the anterior region, for all three stimuli. The P3a amplitude in the posterior region was higher for the PD-N group, across all stimuli for both the easy and hard task. The PD-N participants took longer to respond to the target stimulus than the HC in both the easy and hard task. These results provide a novel contribution to the literature into examining the effect of task difficulty in PD. Further research into a larger sample size and inclusion of cognitively impaired individuals with PD would strengthen these findings in the future.

Chapter 5: Visual oddball task: Comparison of event-related-potentials across cognitive groups

5.1 Introduction

Parkinson's disease (PD) affects multiple neural pathways in the brain and is now acknowledged to be more than a motor disorder (J. G. Goldman & Postuma, 2014). Cognitive decline in PD has significant implications for functioning as well as personal care, caregiver burden, and health-related costs (Antonini et al., 2012; Jones et al., 2017). Depending on longevity, as many as 80% of PD patients progress to dementia (PDD) within 20 years of disease diagnosis (Aarsland et al., 2017; Chaudhuri & Schapira, 2009). Establishing suitable biomarkers for cognitive decline in PD is needed to characterize cognition for these patients in the future (Lanskey et al., 2018).

As described in Chapter 3, electroencephalogram (EEG) could provide a low-cost, non-invasive biomarker for cognition in patients with PD (Geraedts et al., 2018a). An approach to investigate potential biomarkers is through assessing event related potentials (ERPs) associated with cognitively relevant stimuli (Linden, 2005; Squires et al., 1975; Sur & Sinha, 2009). In oddball tasks, the target stimulus occurs infrequently relative to non-target stimuli produces a P300 (P3b); P3b has been associated with global levels of cognitive ability in PD (Adamski et al., 2016). If a second, infrequent stimulus is used as a distractor, a P3a ERP is found which has been associated with attentional processing and executive function in PD (Adamski et al., 2016). Chapter 4 examined the effect of task difficulty using two versions of a three-stimulus visual oddball task ('easy' and 'hard) in a group of PD-N and healthy control (HC) participants. The current study used only the 'easy' version of the three-stimulus visual oddball task to assess group differences and suitable markers for different levels of cognitive status in PD. The use of only the easy task ensured that cognitively-impaired participants could perform and complete the task due to the larger size difference between stimuli.

Previous studies have reported mixed findings regarding the amplitude and latency of P300 components (i.e., P3a and P3b) in three-stimulus visual oddball tasks. A review by Seer et al. (2016) reported studies that found P3b latency is prolonged after

the presentation of a target stimulus for non-demented PD groups compared to the HC groups (Bocquillon et al., 2012; F. Li et al., 2015; Toda et al., 1993). Studies that included patients with PDD and used a three-stimulus visual oddball task also reported that P3b latency was prolonged compared to HCs (Gaudreault et al., 2013; Tachibana et al., 1992; Wang et al., 1999). These findings may reflect changes that happen at a later stage of the disease process (Tanaka et al., 2000; Toda et al., 1993). In addition, Tanaka et al. (2000) and Toda et al. (1993) found no significant differences between non-dementing PD patients and their HC group for the P3b target latency. In regards to P3a latency findings in three-stimulus visual oddball tasks, all studies except one reported no difference between the non-dementing PD and HC groups after the presentation of a distractor stimulus (Bocquillon et al., 2012; Gaudreault et al., 2013; M. Li et al., 2005; Tachibana et al., 1992; Wang et al., 2000). Furthermore, Zeng, Hirata, Tanaka, Hozumi, and Yamazaki (2002) looked at whether there were insufficient processing resources when evaluating an ERP paradigm and reported that there was an increase in P3a latency for non-demented PD patients compared with HCs.

Prior literature has reported that the P3b target amplitude in three-stimulus visual oddball tasks shows no difference between participants who were classified as non-dementing PD (i.e. did not meet criteria for PDD), compared to HCs (Bocquillon et al., 2012; Gaudreault et al., 2013; Tachibana et al., 1992; Toda et al., 1993; Wang et al., 1999). However, two studies that used a three-stimulus visual oddball task reported a reduction in P3b amplitude for the target stimuli in the non-dementing PD groups, compared to the HC groups (Kaufman et al., 2016; M. Li et al., 2005). In comparison, the P3a amplitude showed no change overall between non-demented PD and HC groups (Bocquillon et al., 2012; Gaudreault et al., 2013; Tachibana et al., 1992; Toda et al., 1993; Zeng et al., 2002). However, several studies have reported a reduction in P3a amplitude for the non-demented PD group in comparison to the HC group (Kaufman et al., 2016; M. Li et al., 2005; Wang et al., 2000).

Overall, in the three-stimulus visual oddball task literature, the majority of studies report no differences between non-demented PD patients and HC participants. However one study reported that cognitively-intact PD patients (i.e., do not meet the MDS Task Force Level II criteria for PD-MCI) display an increased P3a and P3b latency, and

a reduced P3a and P3b amplitude, compared to HCs (Ozmus et al., 2017). This variation in previous findings indicates discrepancies in the literature, which our study aimed to investigate by making a direct comparison across a wide spectrum of cognition in PD.

The present study used a three-stimulus visual oddball task to compare HCs with patients classified as PD-N, PD-MCI, or PDD, using the NZBRI criteria. We examined both conventional ERP measures of latency and amplitude of P3b and P3a. There is still considerable variation within the MDS criteria for PD-MCI (Hoogland et al., 2017; Wood et al., 2016). Here, PD-MCI was specified using ten neuropsychological tests have been previously found to identify patients who were at high risk of progression to PDD (Myall et al., 2020). Evidence of changes in this PD-MCI patient group, but not in the PD-N group, may suggest biomarkers associated with cognitive decline in people at risk of PDD.

5.2 Method

5.2.1 Participants

PD patients were classified with a PD-N or PD-MCI status based on performance at 1.5 SD below normative data on any two of ten neuropsychological test measures that the NZBRI shown to select a PD-MCI status with a high risk of progression to PDD (Myall et al., 2020). The PD-MCI criteria were consistent with MDS Level II criteria by requiring two tests from each of the five cognitive domains (executive function, attention, episodic memory, visuoperceptual, and language) and no significant decline in everyday function (Litvan et al., 2012). These criteria for classifying cognition were outlined in Section 2.5. Table 5.2 lists the ten neuropsychological test variables used (in bold); performance on other neuropsychological tests undertaken by participants are provided for comparison, but these were not used to define PD-MCI. PDD status was established using MDS criteria and previous neuropsychological testing (Bruno Dubois et al., 2007b); not all of these patients received a full neuropsychological assessment within six-months of their EEG session, but PDD status was verified in brief assessments conducted at the time of the EEG session. The NZBRI conducts only short assessments for PDD patients at six-monthly intervals to monitor status and cognition. This short

assessment includes the MoCA, cardiovascular health assessment, Hospital Anxiety and Depression Scale (HADS), Geriatric Depression Scale (GDS), UPDRS III, and a hallucinations questionnaire. HC participants also completed comprehensive neuropsychological testing to verify that they were not cognitively impaired.

A convenience sample of 126 participants, comprising 102 PD and 24 HC, was recruited over 2017-2020 from the New Zealand Brain Research Institute (NZBRI) Longitudinal Progression study. Participants were excluded if they had any other neurological conditions, previous deep brain stimulation, any metal plates in the head region, previous history of major psychiatric illness, or drug or alcohol abuse. Non-demented participants received a comprehensive battery of neuropsychological tests, which was used to identify cognitive ability of participants. Three PD participants did not complete the neuropsychological assessments and were excluded. The remainder of participants were classified into PD-N (N = 44), PD-MCI (N = 40), and PDD (N = 15). PD participants received at least 10 neuropsychological tests, but 2 participants had 9 test scores and another 2 had 8 test scores. These participants were included in the data analysis. Most HC participants (N = 22) also received the same battery of neuropsychological tests. All participants had normal or corrected-to-normal vision. All PD participants continued their medication regime during the current study. The Northern B Health and Disabilities Ethics Committee approved the study, including consent prior to the EEG session. Participants were reimbursed for their travel costs.

EEG data were recorded within a six-month window of the comprehensive neuropsychological testing for non-demented patients; 15 participants did not meet this criterion and were excluded. There were 80 PD participants with 10 test scores, 2 had 9 test scores and 2 had 8 test scores. Problems with EEG recordings resulted in a further 21 participants being excluded. The final sample comprised 87 participants across the four groups (Figure 5.1). All participants had normal or corrected-to-normal vision and continued their usual medication regime during all assessments. All PD participants were tested during “on” periods of medication and assessments were re-scheduled if

the participant reported that they were experiencing an “off” medication episode. The flow of participants included for this study is summarized in Figure 5.1.

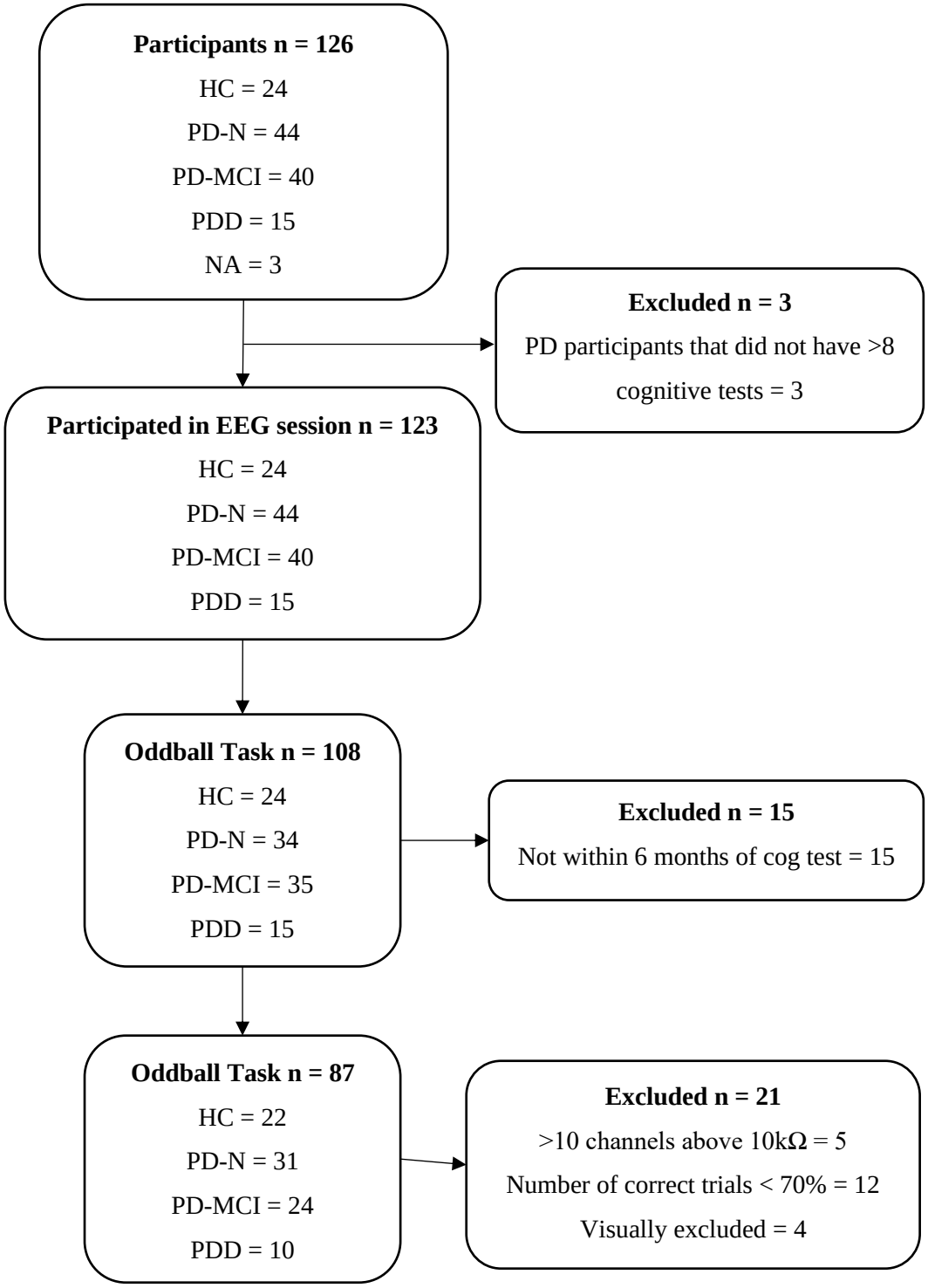

Figure 5.1 STARD chart for participants – comparison of PD cognitive status on the oddball task.

5.2.2 EEG Recordings

EEG collection and recordings followed the same procedure as in Section 4.2.2. Participants were instructed to complete the easy version of the three-stimulus visual oddball task (outlined in Section 4.2.2), for approximately 25 min. EEG recordings were obtained directly after a 10-min eyes-closed resting state condition. Practice trial details and omission rates are the same as outlined in Section 4.2.2. Twelve participants were unable to complete at least 70% of trials and were therefore excluded from the analyses.

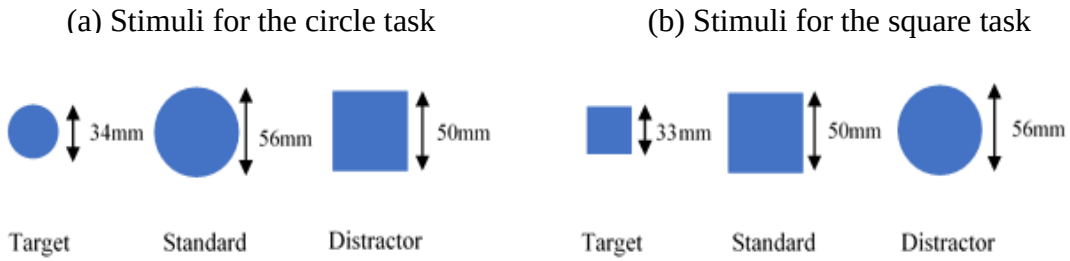

Figure 5.2 Visual oddball subtasks using (a) circle target subtask and (b) square target subtask.

5.2.3 EEG Analysis

The initial EEG analysis was the same as Section 4.2.3. Five participants were excluded from the analysis due to more than 10 electrodes being identified as "noisy" (had an impedance of greater than 10 kΩ). A further 4 participants were visually excluded from the analysis of there was no visible P300. Latency of the P300 was taken between 200—900 ms.

ERPs for the amplitude and latency were assessed both globally over the whole scalp and over electrode-defined regions for the oddball task. The regions used in this study were defined as Anterior, Central and Posterior regions and are outlined in Chapter 4, section 4.2.3. ERP waveforms were averaged across electrodes. Grand averages and reaction times were also assessed.

5.2.4 Statistical Analysis

R version 3.6.3 was used to conduct statistical analyses. Median reaction time was analysed across the whole electrode space and compared across the four groups using a one-way ANCOVA with age and sex as covariates. As neither age nor sex were statistically significant for reaction time (all $F < 0.04$, $df = 1, 83$, $p > 0.85$), the unadjusted model was used to report the comparisons.

Amplitude and latency of the P300 component corresponding to each stimulus were analysed separately, resulting in 6 (3 stimuli × amplitude and 3 stimuli × latency) analyses. For each analysis, a three-way ANOVA was used with group as the between-subject factor and region as the repeated measures factor. Significant group main effect or any significant interaction were further explored by post-hoc analysis. Tukey post-hoc comparisons determined pairwise differences between groups and adjusted $p < 0.05$ was considered statistically significant. All confidence intervals are ±95%.

5.3 Results

5.3.1 Participant Demographics and Group Characteristics

The PD and HC groups are described in Table 5.2. Detailed neuropsychological and neuropsychiatric measures in PDD participants are not provided in Table 5.2 for reasons given above, but PDD participants showed lower MoCA scores. Global Z scores are shown, which are based on the average z-scores both across the "ten sensitive cognitive measures" used to define the PD-MCI group and, for comparison, the twenty-one neuropsychological tests used previously at the NZBRI to summarise cognition in patients with PD-MCI. The Global Z score for the twenty-one tests were calculated by averaging each domain before computing an average of those scores. There were no statistically significant differences between groups for education. Although the neuropsychological test scores for the PD groups were in the normal range, the HC group performed better on all tests except Premorbid IQ, GDS and NPI. There were, however, significant differences between group means for the three PD groups for UPDRS III, and symptom duration, although when used as covariates in the analysis these did not alter the EEG

findings. The PD-N group was significantly younger than the other three groups. All confidence intervals are ±95%.

5.3.2 Reaction Time

The median reaction times for the four groups are shown in Figure 5.3. The median reaction time was shortest in the HC group and progressively increased across PD-N, PD-MCI and PDD groups (Group, $F(3,84) = 3.46$, $p < 0.05$). Post-hoc Tukey comparisons showed the reaction time of HCs was shorter than that of PD-MCI group (Figure 5.3). The median reaction times produced very large Cohen d effect size for the difference between the HC and the PD-MCI groups (d = -0.89, CI = -1.48, -0.29). Although the average reaction time progressively increased from PD-N to PDD, there was no evidence of a significant difference between any PD groups (Table 5.1).

Table 5.1 Median Reaction Time: Group comparisons.

Group	Difference (SE)	t value	p value	Effect Size (±95%CI)	
				Unadjusted	Adjusted for age, UPDRS III and LEDD
HC - PD-N	-0.04 (0.02)	-1.76	0.302	-0.48 (-1.04, 0.07)	-
HC - PD-MCI	-0.08 (0.02)	-3.10	0.014	-0.89 (-1.48, -0.29)	-
HC - PDD	-0.07 (0.03)	-1.95	0.215	-0.80 (-1.63, -0.31)	-
PD-N - PD-MCI	-0.03 (0.02)	-1.52	0.430	-0.40 (-0.94, 0.13)	-0.38 (-0.95, -0.18)
PD-N - PDD	-0.03 (0.03)	-0.80	0.854	-0.32 (-1.11, 0.47)	-0.29 (-1.12, 0.53)
PD-MCI - PDD	-0.01 (0.03)	-0.21	0.996	-0.09 (-0.72, 0.89)	-0.09 (-0.72, 0.89)

Adjusted for multiple comparisons with Tukey. Difference values are measures in seconds.
Abbreviations: Participants with PD who have relatively normal cognition (i.e. do not meet the criteria for PD-MCI); PD-MCI = PD with mild cognitive impairment; PDD = PD with dementia

Table 5.2 Demographic, neuropsychological and neuropsychiatric measures for all participants with exclusions (mean ± SD).

Cognitive Group	HC	PD-N	PD-MCI	PDD	p < 0.05
N	23	31	26	8	
Male/Female	14/9	18/13	16/10	7/1	
Mean Age ± SD (years)	75.7±8.5	66.4±6.2	72.3±7.0	73.9±4.4	*
Symptom Duration ± SD (years)	-	8.9±4.6	14.3±7	13.6±6.4	*
LEDD	-	1025±1460	1026±579	1399±580	
Hoehn & Yahr Stage	-	2.1±0.4	2.5±0.5	2.6±0.4	*
UPDRS III	-	26.5±10.6	40.2±12.1	42.6±6.6	*
Education (years)	14.1±2.9	13.4±2.5	12.3±2.3	14.0±2.9	
Reisberg ADL	0.3±0.3	0.5±0.4	1.1±0.6	-	*
MoCA	26.9±2.2	26.4±2.5	23.2±2.4	17.6±5.2	*
Global Z 21 tests	0.79±0.5	0.23±0.54	-0.50±0.41	-	*
Global Z 10 tests	0.61±0.45	0.14±0.42	-0.88±0.54	-	*
Premorbid IQ (WTAR)	113.91±8.48	110.26±11.28	107.79±9.24	111.24±10.67	
GDS	-	0.03±0.18	0.32±0.56	-	
NPI	-	6.87±6.93	6.50±4.15	11.25±5.15	
Executive Function					
Stroop Interference	**0.86±0.59**	**0.31±0.98**	**-0.46±1.19**	**-**	*
Trails B	**0.76±0.72**	**0.51±0.60**	**-0.86±1.38**	**-**	*
Action (verb) Fluency	0.05±1.12	-0.47±1.24	-0.91±1.3	-	*
Letter Fluency	1.25±1.36	0.84±1.5	0.15±1.25	-	*
Category Fluency	1.78±1.05	0.87±1.13	0.15±1.06	-	*
Category Switching	0.93±1.05	0.31±1.13	-0.5±1.06	-	*
Attention					
Digit Ordering	**-0.12±1.37**	**-0.69±0.86**	**-1.58±1.18**	**-**	*
Map Search 1min	**0.27±0.63**	**-0.32±0.79**	**-1.45±0.91**	**-**	*
Stroop Word Reading	0.43±0.54	-0.18±1.29	-0.37±0.70	-	*
Stroop Colour Naming	0.32±0.77	-0.46±1.26	-0.67±0.47	-	*
Digits Forward & Back	1.01±1.05	0.51±1.18	-0.24±0.75	-	*
Trails A	0.88±0.59	0.51±0.62	0.02±0.94	-	*
Episodic Memory					
CVLT II Total Immediate Recall	**1.87±1.03**	**0.90±1.22**	**-0.23±1.23**	**-**	*
Rey Immediate Recall	**1.03±1.51**	**0.74±1.11**	**-0.65±1.61**	**-**	*
CVLT II Long Delay	1.17±0.97	0.37±0.73	-0.23±0.86	-	*
Visuoperceptual					
Rey Copy	**-0.14±0.78**	**-0.23±0.80**	**-1.90±1.08**	**-**	*
Judgement of Line	**0.12±0.83**	**0.21±0.56**	**-0.77±1.23**	**-**	*
VOSP Fragmented Letters	0.54±0.74	0.34±0.73	-0.23±0.92	-	*
Language					
Mattis DRS-2: Similarities	**0.2±0.41**	**0.06±0.53**	**-0.39±0.91**	**-**	*
ADAS-Cog: Language	**-0.02±0.59**	**-0.1±0.66**	**-0.56±0.81**	**-**	*

All pairwise comparisons are different (except sex, LEDD, education, WTAR, GDS, NPI).
Bolded text indicates the ten neuropsychological tests used in Myall et al. (2020) for cognition.
Cognitive measures are z-scores. Abbreviations: ADAS = Alzheimer's Disease Assessment Scale; ADL = Activities of Daily Living; CVLT = California Verbal Learning Test; DRS = Dementia Rating Scale; HC = Healthy Control; MoCA = Montreal Cognitive Assessment; NA = Not Applicable; PD-N = Participants with PD who have relatively normal cognition (i.e. do not meet the criteria for PD-MCI); PD-MCI = PD with mild cognitive impairment; PDD = PD with dementia; SD = Standard Deviation; UPDRS = Unified Parkinson's Disease Rating Scale; VOSP = Visuospatial Object and Space Perception; WTAR = Wechsler Test of Adult Reading

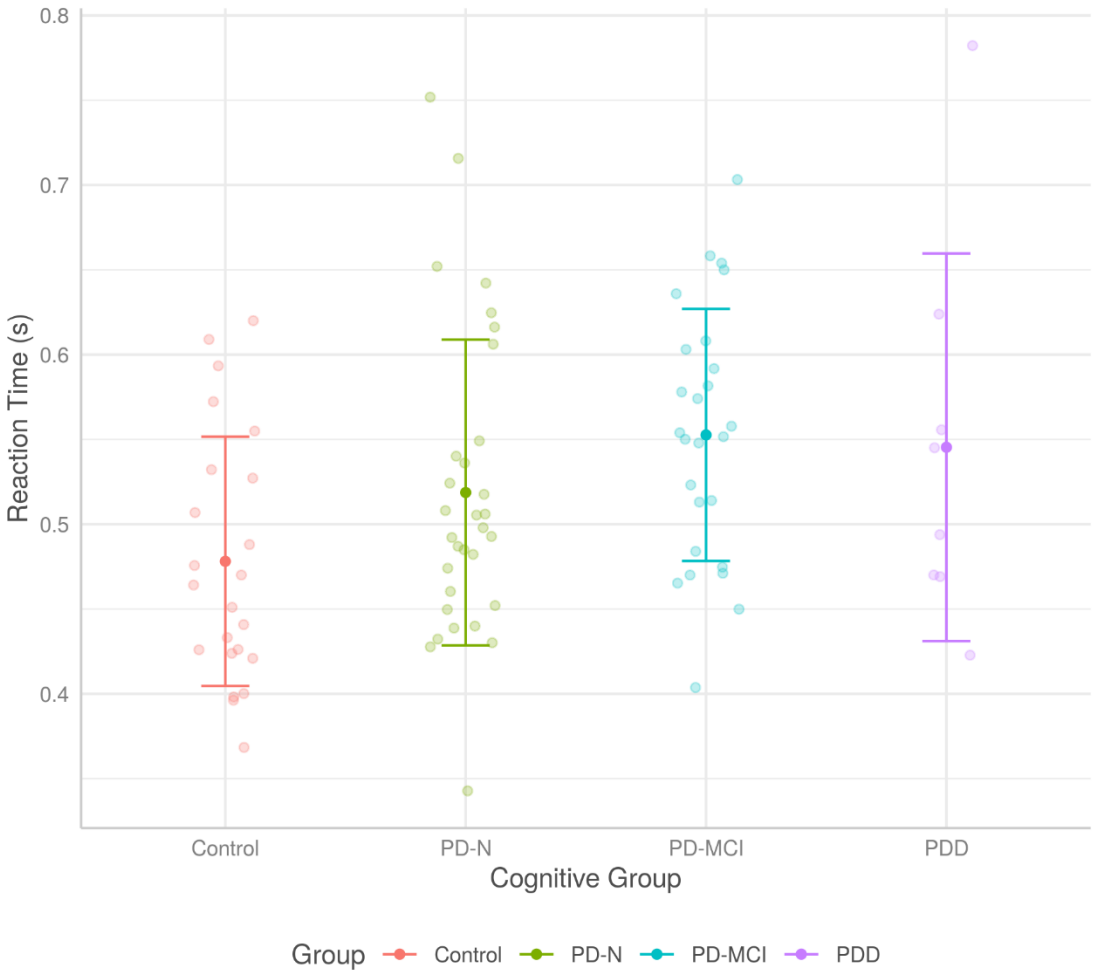

Figure 5.3 Median Reaction time ± SD for the four groups with corresponding individual values.

5.3.3 Grand Average ERPs Waveforms

Grand averages for the ERP waveforms are shown in **Error! Reference source not found.**. Amplitude differences between groups were visually evident in the posterior region for the target, distractor, and standard stimuli. Interestingly, in the posterior region the PD-N group showed the highest P300 amplitude across the three stimuli. Whereas, in the anterior region the HC groups had the highest amplitude for the distractor and standard stimuli.

The subtraction wave for the target-minus-standard, distractor-minus-standard and target-minus-distractor subtraction waves was calculated for the oddball task,

which allowed both P3a and P3b to be localized in both time and space (Figure 5.5 Grand average subtraction wave for all four groups across the three electrode regions.). The subtraction waves calculated minimized the baseline drift for all four participant groups (HC, PD-N, PD-MCI and PDD). Furthermore, the distractor-minus-standard

wave minimised the amplitude of the P3a wave and was smaller than the target-minus-standard and target-minus-distractor.

Figure 5.4 Grand averages for three stimuli for the four groups, across the three electrode regions. Control = Healthy controls; PD-N = PD with relatively normal cognition, PD-MCI = PD with mild cognitive impairment; PDD = PD with dementia.

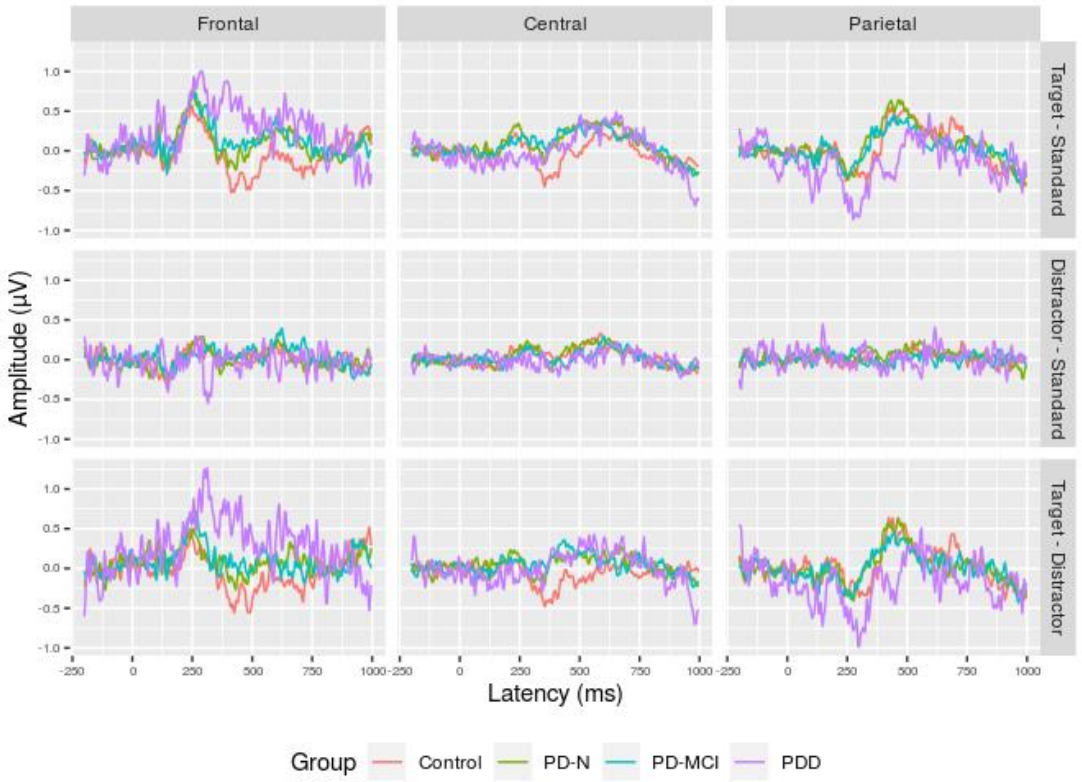

Figure 5.5 Grand average subtraction wave for all four groups across the three electrode regions.

5.3.4 P300 Latency

Latency differences between groups were prolonged in the anterior region and increased in the central and posterior region for all groups, for all stimuli (**Error! Reference source not found.**). All stimuli for the latency produced a significant main effect for region (all $F(2, 168) > 19.10$, all $p < 0.001$), where the latencies were shorter in the posterior region and were gradually prolonged towards the anterior region. There was no significant main effect for Group for any of the stimuli (all $F(3, 83) < 1.43$, $p > 0.24$). There were also no significant Group × Region interactions for any of the three stimuli (all $F(6, 168) < 0.76$, $p > 0.12$). Adjusting for age and sex did not change the results.

For the target stimuli, there was a significant main effect of region ($F(2, 168) = 20.60$, $p = 0.001$). Latency was prolonged in the anterior region compared to the central and posterior. There were no significant differences between groups, although pairwise effect sizes were largest for the PD-MCI and PDD group in the posterior region ($d = -0.70$, CI = -1.60, 0.21). These effect sizes are small to medium at best, and, for interest, pairwise effect sizes are shown in Table 5.3.

There was a significant main effect of region for the distractor stimuli ($F(2, 168) = 41.63$, $p = 0.001$). All four groups showed a reduction in latency across anterior to central and then to posterior electrode regions. Large effect sizes were seen between the HC and PD-MCI group for the anterior region ($d = -0.65$, CI = -1.29, -0.01), and between the HC and PD-MCI group for the central region ($d = -0.59$, CI = -1.23, 0.04). These pairwise effect sizes are shown in Table 5.4.

For the standard stimuli, all four groups showed a reduction in latency across anterior to central and then to posterior electrode regions. Large effect sizes were between the HC and PD-N group for the anterior region ($d = -0.92$, CI = -1.56, -0.29), and between the PD-N and PDD group for the posterior region ($d = 0.66$, CI = -0.20, 1.52) (Table 5.5).

Table 5.3 Target stimuli latency differences in the four groups.

Cognitive Group	Region	Difference	t value	p value	Effect size (±95%CI)
HC - PD-N	Anterior	-88.50	-1.86	0.247	-0.61 (-1.27, 0.05)
HC - PD-MCI	Anterior	-43.86	-0.94	0.785	-0.30 (-0.95, 0.34)
HC - PDD	Anterior	-84.01	-1.26	0.589	-0.58 (-1.50, 0.34)
PD-N - PD-MCI	Anterior	44.64	1.01	0.746	0.31 (-0.30, 0.92)
PD-N - PDD	Anterior	4.49	0.07	1.000	0.03 (-0.30, 0.92)
PD-MCI - PDD	Anterior	-40.15	-0.61	0.928	-0.28 (-1.18, 0.62)
HC - PD-N	Central	-52.98	-1.12	0.681	-0.37 (-1.02, 0.29)
HC - PD-MCI	Central	16.87	0.36	0.984	0.12 (-0.52, 0.76)
HC - PDD	Central	-58.36	-0.88	0.818	-0.41 (-1.32, 0.51)
PD-N - PD-MCI	Central	69.85	1.57	0.396	0.48 (-0.13, 1.10)
PD-N - PDD	Central	-5.38	-0.08	1.000	0.04 (-0.93, 0.86)
PD-MCI - PDD	Central	-75.23	-1.15	0.661	-0.52 (-1.42, 0.38)
HC - PD-N	Posterior	14.12	0.30	0.991	0.10 (-0.55, 0.75)
HC - PD-MCI	Posterior	35.89	0.77	0.869	0.25 (-0.39, 0.89)
HC - PDD	Posterior	-64.38	-0.97	0.769	-0.47 (-1.36, 0.47)
PD-N - PD-MCI	Posterior	21.77	0.49	0.961	-0.15 (-0.46, 0.76)
PD-N - PDD	Posterior	-78.50	-1.20	0.630	-0.54 (-1.45, 0.36)
PD-MCI - PDD	Posterior	-100.27	-1.53	0.423	-0.70 (-1.60, 0.21)

Abbreviations: PD-N = Participants with PD who have relatively normal cognition (i.e. do not meet the criteria for PD-MCI); PD-MCI = PD with mild cognitive impairment; PDD = PD with dementia; C.I = Confidence interval

Table 5.4 Distractor stimuli latency differences in the four groups.

Cognitive Group	Region	Difference	t value	p value	Effect size (±95%CI)
HC - PD-N	Anterior	-60.73	-1.36	0.528	-0.44 (-1.08, 0.20)
HC - PD-MCI	Anterior	-90.93	-2.06	0.171	-0.65 (-1.29, -0.14)
HC - PDD	Anterior	-71.72	-1.14	0.666	-0.52 (-1.41, 0.38)
PD-N - PD-MCI	Anterior	-30.20	-0.72	0.889	0.22 (-0.81, 0.38)
PD-N - PDD	Anterior	-10.99	-0.18	0.998	-0.08 (-0.96, 0.80)
PD-MCI - PDD	Anterior	19.21	0.31	0.990	0.14 (-0.74, 1.02)
HC - PD-N	Central	-24.98	-0.56	0.944	-0.18 (-0.81, 0.46)
HC - PD-MCI	Central	-82.72	-1.87	0.243	-0.59 (-1.23, -0.04)
HC - PDD	Central	-77.70	-1.23	0.606	-0.56 (-1.46, 0.34)
PD-N - PD-MCI	Central	-57.74	-1.38	0.514	-0.41 (-1.01, 0.18)
PD-N - PDD	Central	-52.72	-0.85	0.830	-0.38 (-1.26, 0.50)
PD-MCI - PDD	Central	5.02	0.08	1.000	0.04 (-0.84, 0.91)
HC - PD-N	Posterior	8.71	0.19	0.997	0.06 (-0.57, 0.70)
HC - PD-MCI	Posterior	-0.14	0.00	1.000	-0.001 (-0.63, 0.62)
HC - PDD	Posterior	-7.66	-0.12	0.999	-0.06 (-0.95, 0.84)
PD-N - PD-MCI	Posterior	-8.84	-0.21	0.997	-0.06 (-0.66, 0.53)
PD-N - PDD	Posterior	-16.36	-0.26	0.994	-0.12 (-0.99, 0.76)
PD-MCI - PDD	Posterior	-7.52	-0.12	0.999	-0.05 (-0.93, 0.82)

Abbreviations: PD-N = Participants with PD who have relatively normal cognition (i.e. do not meet the criteria for PD-MCI); PD-MCI = PD with mild cognitive impairment; PDD = PD with dementia; C.I = Confidence interval

Table 5.5 Standard stimuli latency differences in the four groups.

Cognitive Group	Region	Difference	t value	p value	Effect size (±95%CI)
HC - PD-N	Anterior	-121.40	-2.97	0.017	-0.93 (-1.56, 0.29)
HC - PD-MCI	Anterior	-58.64	-1.45	0.471	-0.45 (-1.06, 0.17)
HC - PDD	Anterior	-34.75	-0.60	0.931	-0.27 (-1.13, -0.60)
PD-N - PD-MCI	Anterior	62.76	1.64	0.359	0.48 (-0.10, 1.06)
PD-N - PDD	Anterior	86.65	1.53	0.422	0.66 (-0.20, 1.52)
PD-MCI - PDD	Anterior	23.90	0.42	0.975	0.28 (-0.67, 1.04)
HC - PD-N	Central	-20.87	-0.51	0.956	-0.16 (-0.77, -0.46)
HC - PD-MCI	Central	-46.21	-1.14	0.664	-0.35 (-0.96, -0.26)
HC - PDD	Central	-39.20	-0.68	0.905	-0.30 (-1.17, 0.57)
PD-N - PD-MCI	Central	-25.34	-0.66	0.911	-0.19 (-0.77, 0.38)
PD-N - PDD	Central	-18.33	-0.32	0.988	-0.14 (-0.99, 0.71)
PD-MCI - PDD	Central	7.01	0.12	0.999	0.05 (-0.80, 0.91)
HC - PD-N	Posterior	17.86	0.44	0.972	0.14 (-0.48, 0.75)
HC - PD-MCI	Posterior	14.64	0.36	0.984	0.11 (-0.50, 0.72)
HC - PDD	Posterior	-32.62	-0.57	0.942	-0.25 (-1.12, 0.62)
PD-N - PD-MCI	Posterior	-3.22	-0.08	1.000	-0.02 (-0.60, 0.55)
PD-N - PDD	Posterior	-50.47	-0.89	0.810	-0.38 (-1.24, 0.47)
PD-MCI - PDD	Posterior	-47.26	-0.83	0.840	-0.36 (-1.22, 0.50)

Abbreviations: PD-N = Participants with PD who have relatively normal cognition (i.e. do not meet the criteria for PD-MCI); PD-MCI = PD with mild cognitive impairment; PDD = PD with dementia; C.I = Confidence interval

5.3.5 P300 Amplitude

Amplitude differences between groups were lower in the central region and increased in the posterior region for all stimuli (Figure 5.6). All stimuli for the amplitude produced a significant main effect for the Region (All $F(2, 168) > 19.10$, all $p < 0.001$), where the amplitudes were highest in the posterior region for all groups. There was no significant main effect for Group for any of the stimuli (All $F(3, 83) < 0.23$, $p > 0.87$). There were also no significant Group × Region interactions for any of the three stimuli (all $F(6, 168) < 2.03$, $p > 0.06$). The findings remained the same when age and sex were included as covariates.

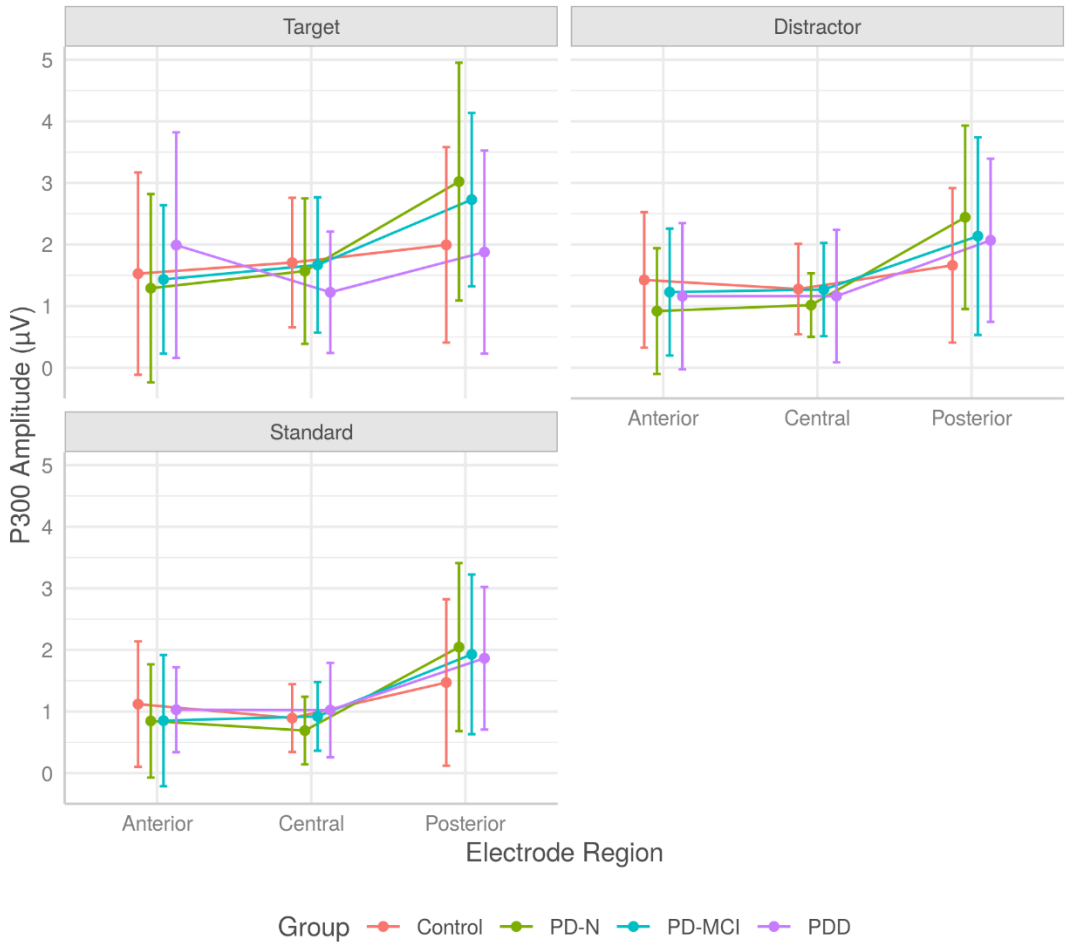

Figure 5.6 Mean amplitude ± SD for three stimuli in the four groups, across the three electrode regions.

For the target stimuli, the PD-N group showed an increase in amplitude across anterior to central and then to posterior electrode regions. There was a trend towards significance for the Group × Region interaction ($F(6, 168) = 2.03$, $p = 0.06$). Post-hoc analysis of the Group × Region interaction revealed a simple main effect of Region for the PD-N and PD-MCI group ($p < 0.001$); there was no regional decline for the HC ($p = 0.47$) and PDD groups ($p = 0.44$) (Table 5.6). Large effect sizes were seen between PD-N and the PDD group ($d = 0.81$, CI = -0.10, 1.72) and between the HC and PD-N groups ($d = -0.70$, CI = -1.37, -0.04) in the posterior region.

For the distractor stimuli, the PD-N, PD-MCI, and PDD groups showed an increase in amplitude in the posterior region and a decrease in the central region. There

were no significant differences between groups, although pairwise effect sizes were largest for the HC and PD-N group for the posterior region (d = -0.74, CI = -1.34, -0.13). These effect sizes were medium to large, and, for interest, pairwise effect sizes are shown in Table 5.7.

For the standard stimuli, the PD-N, PD-MCI and PDD group showed an increase in amplitude in the posterior region compared to the central and anterior regions. There were no significant differences between groups, and pairwise effect sizes were shown in Table 5.8. A large effect size was found between the HC and PD-N groups for the posterior region (d = -0.67, CI = -1.25, -0.08).

Table 5.6 Target stimuli amplitude differences in the four groups.

Cognitive Group	Region	Difference	t value	p value	Effect size (±95%CI)
HC - PD-N	Anterior	0.36	0.84	0.834	0.28 (-0.37, 0.92)
HC - PD-MCI	Anterior	0.14	0.33	0.988	0.11 (-0.53, 0.75)
HC - PDD	Anterior	-0.44	-0.74	0.882	-0.34 (-1.25, 0.57)
PD-N - PD-MCI	Anterior	-0.22	-0.56	0.945	-0.17 (-0.78, 0.44)
PD-N - PDD	Anterior	-0.80	-1.36	0.527	-0.62 (-1.52, 0.29)
PD-MCI - PDD	Anterior	-0.58	-0.98	0.759	-0.45 (-1.35, 0.45)
HC - PD-N	Central	0.26	0.61	0.929	0.20 (-0.45, 0.85)
HC - PD-MCI	Central	0.08	0.20	0.997	0.064 (-0.58, 0.70)
HC - PDD	Central	0.51	0.85	0.830	0.393 (-0.52, 1.31)
PD-N - PD-MCI	Central	-0.18	-0.45	0.971	-0.14 (-0.74, 0.47)
PD-N - PDD	Central	0.25	0.42	0.975	0.19 (-0.71, 1.09)
PD-MCI - PDD	Central	0.42	0.72	0.888	0.33 (-0.57, 1.23)
HC - PD-N	Posterior	-0.91	-2.14	0.145	-0.70 (-1.37, -0.04)
HC - PD-MCI	Posterior	-0.69	-1.65	0.351	-0.54 (-1.18, 0.11)
HC - PDD	Posterior	0.14	0.24	0.995	0.11 (-0.80, 1.02)
PD-N - PD-MCI	Posterior	0.22	0.54	0.948	0.17 (-0.44, 0.77)
PD-N - PDD	Posterior	1.05	1.79	0.282	0.81 (-0.10, 1.72)
PD-MCI - PDD	Posterior	0.83	1.42	0.489	0.65 (-0.26, 1.55)

Abbreviations: PD-N = Participants with PD who have relatively normal cognition (i.e. do not meet the criteria for PD-MCI); PD-MCI = PD with mild cognitive impairment; PDD = PD with dementia; C.I = Confidence interval

Table 5.7 Distractor stimuli amplitude differences in the four groups.

Cognitive Group	Region	Difference	t value	p value	Effect size (±95%CI)
HC - PD-N	Anterior	0.48	1.50	0.442	0.44 (-0.15, 1.04)
HC - PD-MCI	Anterior	0.19	0.59	0.936	0.17 (-0.41, 0.76)
HC - PDD	Anterior	0.26	0.57	0.942	0.24 (-0.59, 1.07)
PD-N - PD-MCI	Anterior	-0.29	-0.97	0.768	-0.27 (-0.82, 0.28)
PD-N - PDD	Anterior	-0.22	-0.50	0.960	0.21 (-1.02, 0.61)
PD-MCI - PDD	Anterior	0.07	0.16	0.999	0.07 (-0.75, 0.88)
HC - PD-N	Central	0.24	0.74	0.883	0.22 (0.37, 0.81)
HC - PD-MCI	Central	0.00	0.00	1.000	0.001 (-0.58, 0.58)
HC - PDD	Central	0.11	0.24	0.995	0.10 (-0.73, 0.33)
PD-N - PD-MCI	Central	-0.24	-0.78	0.864	-0.22 (-1.34, -0.13)
PD-N - PDD	Central	-0.13	-0.28	0.992	-0.12 (-0.93, 0.70)
PD-MCI - PDD	Central	0.11	0.24	0.995	0.10 (-72, 0.92)
HC - PD-N	Posterior	-0.80	-2.48	0.066	-0.74 (-1.34, -0.13)
HC - PD-MCI	Posterior	-0.48	-1.50	0.441	-0.44 (-1.03, 0.15)
HC - PDD	Posterior	-0.41	-0.90	0.807	-0.38 (-1.21, 0.46)
PD-N - PD-MCI	Posterior	0.32	1.05	0.719	0.29 (0.26, 0.85)
PD-N - PDD	Posterior	0.39	0.87	0.822	0.36 (0.46, 1.18)
PD-MCI - PDD	Posterior	0.07	0.16	0.999	0.07 (-0.75, 0.88)

Abbreviations: PD-N = Participants with PD who have relatively normal cognition (i.e. do not meet the criteria for PD-MCI); PD-MCI = PD with mild cognitive impairment; PDD = PD with dementia; C.I = Confidence interval

Table 5.8 Standard stimuli amplitude differences in the four groups.

Cognitive Group	Region	Difference	t value	p value	Effect size (±95%CI)
HC - PD-N	Anterior	0.18	0.64	0.920	0.19 (-0.39, 0.76)
HC - PD-MCI	Anterior	0.24	0.82	0.847	0.24 (-0.34, 0.81)
HC - PDD	Anterior	0.07	0.18	0.998	0.07 (-0.74, 0.89)
PD-N - PD-MCI	Anterior	0.05	0.19	0.998	0.05 (-0.49, 0.59)
PD-N - PDD	Anterior	-0.11	-0.27	0.993	-0.11 (-0.91, 0.69)
PD-MCI - PDD	Anterior	-0.16	-0.40	0.979	-0.16 (-0.97, 0.64)
HC - PD-N	Central	0.11	0.39	0.980	0.11 (-0.46, 0.69)
HC - PD-MCI	Central	-0.06	-0.21	0.997	-0.06 (-0.63, 0.51)
HC - PDD	Central	-0.15	-0.36	0.984	-0.15 (-0.96, 0.67)
PD-N - PD-MCI	Central	-0.17	-0.63	0.921	-0.17 (-0.71, 0.37)
PD-N - PDD	Central	-0.26	-0.64	0.917	-0.26 (-1.06, 0.54)
PD-MCI - PDD	Central	-0.09	-0.22	0.996	-0.09 (-0.89, 0.72)
HC - PD-N	Posterior	-0.66	-2.29	0.103	-0.66 (-1.25, -0.08)
HC - PD-MCI	Posterior	-0.49	-1.69	0.332	-0.49 (-1.07, 0.09)
HC - PDD	Posterior	-0.41	-1.00	0.752	0.41 (-1.23, 0.41)
PD-N - PD-MCI	Posterior	0.18	0.64	0.918	0.18 (-0.36, 0.72)
PD-N - PDD	Posterior	0.25	0.62	0.924	0.25 (-0.55, 1.05)
PD-MCI - PDD	Posterior	0.08	0.19	0.998	0.08 (-0.73, 0.88)

Abbreviations: PD-N = Participants with PD who have relatively normal cognition (i.e. do not meet the criteria for PD-MCI); PD-MCI = PD with mild cognitive impairment; PDD = PD with dementia; C.I = Confidence interval

5.4 Discussion

The main finding from this study was that there were no significant differences between any of the cognitive groups for the P3a (i.e., elicited from distractor) and P3b (i.e., elicited from target) latency as well as for the P3a and P3b amplitude. Although there were no significant differences, P3a and P3b latencies decreased on average across the anterior to central to posterior region for all four groups and all three stimuli. Whereas the P3a and P3b amplitude increased on average from the central to the posterior region for all cognitive groups except for the HC group. The P3b amplitude was highest in the PD-N and PD-MCI group, although these were not significantly different from the HC and PDD group. There was a significant regional effect for all three stimuli for both the latency and amplitude. Lastly, the median reaction time was shortest in the HC group

and progressively increased across PD-N, once patients met the criteria PD-MCI, and especially when they met criteria for PDD.

These cross-sectional findings are in line with other three-stimulus visual oddball studies which looked at P3a and P3b ERP latency and amplitude differences between participant groups and reported no significant differences between P3a latency and P3b amplitude (Bocquillon et al., 2012; Gaudreault et al., 2013; Tachibana et al., 1992; Toda et al., 1993; Wang et al., 1999). Our reaction time findings are also in line with other studies as reaction time is prolonged as cognition declines (Kaufman et al., 2016; Toda et al., 1993; Wang et al., 1999). Thus, it is clear that patients with PD who are cognitively impaired have prolonged reaction times, even though P3a and P3b latencies and amplitudes do not differ between groups.

The standard stimuli had the highest latency in the anterior region for the PD-N group. Large effect sizes accompanied these findings and help strengthen the differences between the pairwise comparisons for the HC and PD-N group. These observations do not accord with previous findings as Toda et al. (1993) reported no significant differences in P300 for the latency. Bocquillon et al. (2015) also reported that the P300 component in PD patients was decreased compared to HCs. However, we did find significant differences between the PD-N and PD-MCI group across region for the target stimuli, between all four groups for the distractor stimuli, and between the HC, PD-N and PD-MCI group for the standard stimuli. These differences suggest that there may be regional changes.

These results do not accord with prior literature as Seer et al. (2016) reported several studies in their review found a reduced P3b amplitude in the PD-N patients (who did not meet the criteria for PD-MCI) compared to HCs (Kaufman et al., 2016; M. Li et al., 2005). As our results differ from the literature, this may suggest that participants were engaging attentively when processing the stimuli and that they have increased focal attention as well (Hagen et al., 2006). This suggests that PD-N participants may unconsciously be deploying higher attentional resources to the processing of the target stimulus than the HC, which may be a compensation of the degeneration that is starting

to take place (Green et al., 1996). The same results were also found for the target and standard stimuli in the posterior region.

We did, however, find a linear association between median reaction time and cognitive group for all participants, indicating that as cognition declined, reaction time increased. This suggests that the PD participants are performing slower than the HC at the group level. The association between reaction time and cognition has been investigated previously, although this has only been examined in a study that looked at a non-demented PD group, a PDD group and an HC group (Toda et al., 1993), as well as two other studies that compared a non-demented PD group and an HC group (Kaufman et al., 2016; Wang et al., 1999). The findings from our study suggest that as individuals progress to dementia, their reaction times increase, and they take longer to respond to the stimuli. If this reflects longitudinal changes, reaction times may help to predict an individual's future level of cognitive impairment irrespective of ERP measures.

There are strengths of our study which outline the novel contribution to the literature. No prior research has looked at the relationship between ERPs from a three-stimulus visual oddball task and a full spectrum of cognition in PD. Prior studies have only examined differences between non-dementing and dementing participants (Bocquillon et al., 2012; Seer et al., 2016; Toda et al., 1993; Wang et al., 1999). This gives the study an advantage to produce initial research that investigates the relationship between a full range of cognitive groups in PD and P300 components elicited from different stimuli. Another strength to the study is the criteria used to classify cognition. As Myall et al. (2020) has reported, people with PD who meet the criteria for PD-MCI are at an increased risk of progressing to dementia. We used a range of PD participants with varying cognition and made a direct comparison between a PD-N, PD-MCI and PDD group, and compared them to HC participants to determine any differences between groups. This NZBRI criteria may not show significant separation between the HC and PD-N group, however it may show potential for progression to PDD in the future.

The methodological choices were constrained by the small number of PDD participants that were included in the study. These have previously been outlined in

Chapter 4. The main limitation of the study is the minimal number of trials for each stimulus. This is because each participant completes the easy task which have 50 target stimuli, 50 distractor stimuli and 500 standard stimuli each. When analysed all epochs that have artefacts or incorrect responses are rejected and only the correct, clean responses are analysed. In future studies it may be beneficial to add more trials to each task or have the participant complete the task until they correctly identify a certain number of correct stimuli to complete the task. This is to ensure there are enough data to analyse and each participant has the same number of trials to directly compare groups accurately. For instance, Kaufman et al. (2016) used 600 trials in their task, whereas Toda et al. (1993) used 256-320 trials.

The lack of significant differences seen in this task may be attributed to the difficulty of task used in the EEG session. As described in Chapter 4, task difficulty was examined between an easy and hard task to determine any differences. We made the decision to use the easy task only to investigate differences between groups. This was to ensure cognitively-impaired participants were able to complete the task, although this task did not produce many significant results. The use of the easy task may have masked the effects between groups if the task was too simple and participants did not need to use as much attention to respond to the target stimulus. In future, using another task, such as the hard task may be beneficial to identify differences between groups, especially in the PD-MCI and PDD group.

Finally, more PDD participants would increase the statistical power. There were substantially fewer PDD participants than any of the other three cognitive groups, which was due to the complications associated with PDD and recruitment. This was mainly due to the severity of their condition and the inability to physically come into the Institute for the EEG session. Transporting EEG equipment is relatively difficult and may introduce confounding factors, which limits the experiment to being conducted onsite. As a result, those participants who are in care or have severe motor or cognitive disabilities tend to decline participation due to the effort required to come in and participate in the session. For future studies, adding more participants to this group would be a good way to determine whether with a larger sample size the same results were found or whether there was a difference with more participants having completed both

the EEG and neuropsychological sessions. However, the results in this chapter do not support doing any further study on ERPs in PD due to the non-significant findings between P3a and P3b latency and amplitude when making a direct comparison between a HC, PD-N, PD-MCI, and PDD group.

5.5 Conclusion

This study found no significant differences between P3a distractor and P3b target latency or amplitude between the HC, PD-N, PD-MCI, and PDD group. Median reaction times differed between groups and was shortest in the HC group and increased in the PD-N, PD-MCI and PDD group. These results provide a novel contribution to the literature into determining whether ERPs could be used as a measure to characterise cognition in PD. Further research into a larger sample of PDD participants and potentially the hard version of the task across the cognitive groups would help to strengthen these findings.

Chapter 6: Spectral power and individual alpha frequency in the resting state

6.1 Introduction

As described in Chapter 2, PD is a progressive neurodegenerative disorder that is frequently associated with cognitive decline, which leads to dementia in as many as 80% of patients within 20 years (Aarsland et al., 2017; J. Goldman & Litvan, 2011; Meireles & Massano, 2012; Weintraub et al., 2018). Like elsewhere, the prevalence of PD in New Zealand is expected to double over the next twenty years (Dorsey & Bloem, 2018; Myall et al., 2017). Given that PD substantially impacts quality of life and increases care-giver burden, it is important to identify reliable biomarkers of cognition to potentially predict and track future cognitive decline (Aarsland et al., 2017). Such biomarkers could be ultimately beneficial for targeted medication and therapeutic interventions. There has been increasing interest in using EEG measures for this purpose, due to its simple and non-invasive technique (Al-Qazzaz et al., 2014; Gao & Wu, 2016; Yi, Wang, Deng, & Wei, 2017).

Spectral power and individual alpha frequency (IAF) are two key metrics derived from EEG data, as previously outlined in Chapter 3. In terms of spectral power for the common frequency bands, prior cross-sectional research reported an increase in theta band power and a reduction in alpha band power in PD-MCI and PDD patients (Caviness et al., 2007; Caviness et al., 2016; Chaturvedi et al., 2019). In addition, Ponsen et al. (2012) and Han et al. (2013) reported an increase in delta band power in PD patients who were not cognitively impaired (did not meet MDS Level II criteria for PD-MCI). A previous review of potential biomarkers associated with cognitive decline in PD concluded that a decrease in the power of alpha band and an increase in the relative theta/alpha power ratio are associated with progression to PDD (Cozac et al., 2016). Only one of the included studies assessed group differences in relative spectral power directly across a spectrum of healthy control (HC), PD-N, PD-MCI, and PDD patients (Fonseca et al., 2009). They found no significant difference between the PD-N and HC group. Although there was an increase in posterior relative spectral power in the theta

band for participants with PD-MCI and PDD, as well as for the posterior delta band in participants with PDD. However, the sample size in the aforementioned study of 10 PD-MCI and 7 PDD patients was relatively small (Fonseca et al., 2009).

IAF is the peak alpha frequency of EEG, which is prominent in the posterior region during eyes-closed resting wakefulness. IAF has previously been used to examine its association with cognitive status in PD and is usually taken to mean the frequency with the peak power in alpha range of frequencies (Grandy et al., 2013). One study reported a constant IAF over a 4-year period in HC, whereas the unimpaired PD group showed a decrease in IAF frequency (Dubbelink et al., 2013). To our knowledge, however, no study has examined IAF differences by directly comparing HC with a wide spectrum of cognitive ability (i.e., HC PD-N, PD-MCI and PDD groups). One study reported lower IAF in PDD patients compared to a HC group, (Babiloni et al., 2017a). Evidence on the relative impact of PD with and without cognitive impairment on IAF, rather than comparisons between PD-MCI and HC or HC and cognitively unspecified other than non-dementing PD is lacking.

We therefore examined EEG spectral power and IAF in PD patients classified as PD-N, PD-MCI, and PDD, relative to a HC sample. The standard approach for a Level II PD-MCI diagnosis is to use any two tests to represent performance in each of five cognitive domains, but this patient group often includes between 20% to 37% of patients who revert to PD-N status (Saredakis, Collins-Praino, Gutteridge, Stephan, & Keage, 2019). This arises because PD-MCI groups can be based on markedly variable criteria (Dalrymple-Alford et al., 2011; Liepelt-Scarfone et al., 2011), even when using the MDS Task Force guidelines (Saredakis et al., 2019). To derive a group of patients who were more likely to stay either stable or decline to PDD, we identified PD-MCI patients using a specific selection of 10 neuropsychological tests, with 2 tests in each of 5 cognitive domains. We have shown that these tests are sensitive for identifying PD-MCI patients who have an 8-fold relative risk of progression to PDD compared to non-MCI patients over a 4-year period (Myall et al., 2020). The primary aim of a PD-MCI status is to capture patients at high risk of PDD, so our approach is well suited to determine the EEG measures that best discriminate at-risk PD-MCI patients from both PD-N and HC participants.

6.2 Method

6.2.1 Participants

PD patients were classified with a PD-N or PD-MCI status based on the NZBRI criteria outlined in Section 2.7. Table 6.1 lists the ten neuropsychological test variables used (in bold); performance on other neuropsychological tests undertaken by participants are provided for comparison, but these were not used to define PD-MCI. A PDD status was established using MDS criteria and previous neuropsychological testing (Bruno Dubois et al., 2007b); not all of these patients received a full neuropsychological assessment within six-months of their EEG session, but PDD status was verified in brief assessments conducted at the time of the EEG session. The NZBRI conducts only short assessments for PDD patients at six-monthly intervals to monitor status and cognition. This short assessment includes the MoCA, cardiovascular health assessment, Hospital Anxiety and Depression Scale (HADS), Geriatric Depression Scale (GDS), UPDRS III, and a hallucinations questionnaire. HC participants also completed comprehensive neuropsychological testing to verify that they were not cognitively impaired.

A convenience sample of 166 participants, comprising 126 PD and 40 HC, was recruited between 2017-2020 from the New Zealand Brain Research Institute (NZBRI) Longitudinal Progression study. Participants were excluded if they had any other neurological conditions, had previous deep brain stimulation or any metal plates in the head region or previous history of major psychiatric illness, drug or alcohol abuse. Non-demented participants received a comprehensive battery of neuropsychological tests, which was used to identify cognitive ability of participants. Three participants did not complete neuropsychological tests and were excluded. The remainder of participants were classified into PD-N (N = 56), PD-MCI (N = 50), and PDD (N = 17). PD participants received at least 10 neuropsychological tests, but two completed 8 tests and two completed 9 tests. These participants were included in the analyses.

EEG data were recorded within a six-month window of the comprehensive neuropsychological testing for non-demented patients; 11 participants did not meet this criterion and were excluded. There were 102 PD participants with 10 test scores, 2 had 9 test scores (missing ADAS-Cog Language) and 2 had 8 test scores (missing Rey Copy

and Rey Immediate recall). Problems with EEG recordings resulted in a further 27 participants being excluded. There was a final sample size of 125 participants across the four groups (Figure 6.1). All participants had normal or corrected-to-normal vision and continued their usual medication regime during all assessments. All PD participants were tested during "on" periods of medication and assessments were re-scheduled if the participant reported that they were experiencing an "off" medication episode. The Northern B Health and Disabilities Ethics Committee approved the study including consent prior to the EEG session. Participants were reimbursed for their travel costs. The flow of participants included for this study is summarized in Figure 6.1.

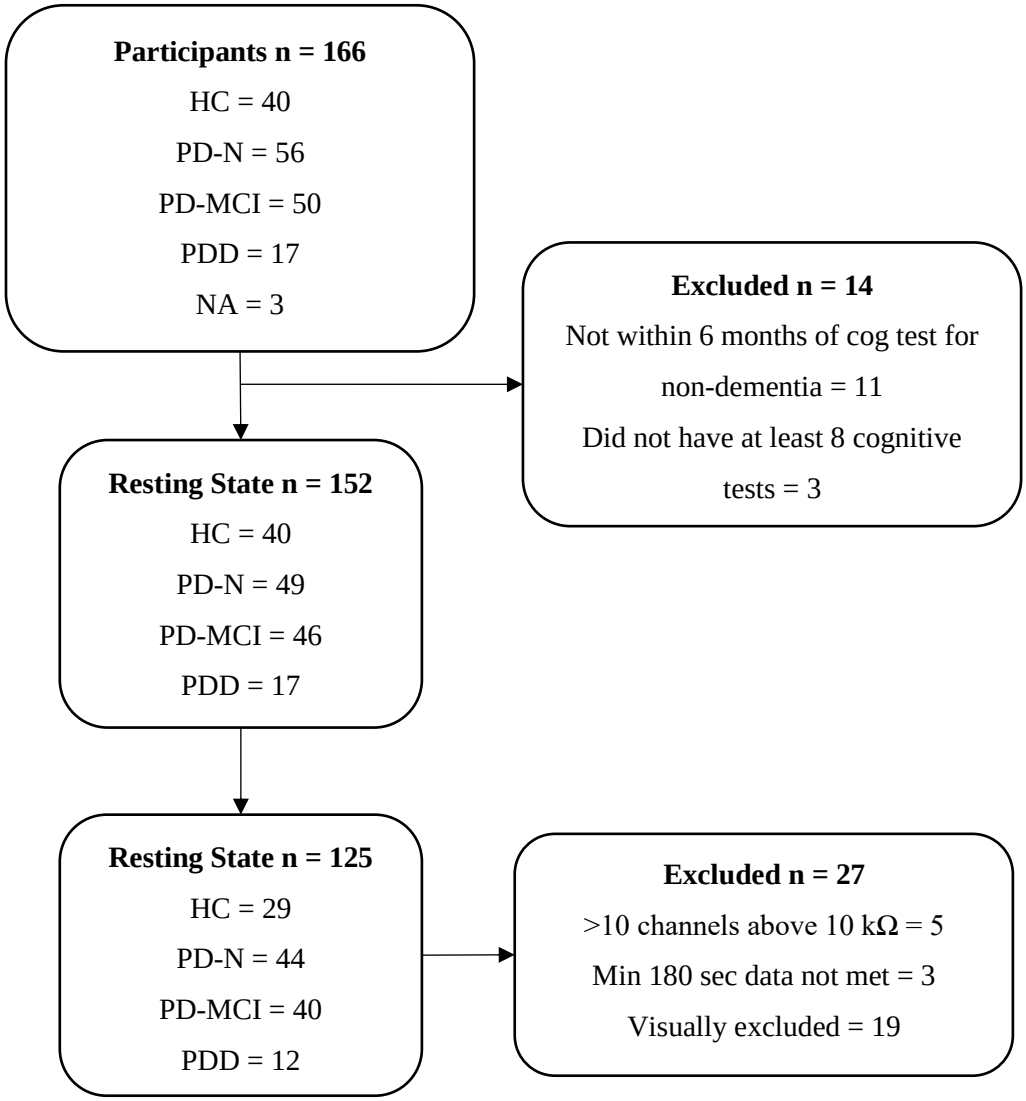

Figure 6.1 STARD chart for participants.

6.2.2 EEG Recordings

Participants completed the EEG session at the NZBRI. Nine minutes of resting state EEG was acquired using a 64-electrode Neuroscan Compumedics Quik-cap (Compumedics Neuromedical Supplies, Abbotsford, Australia) while the participant sat comfortably, but as still as feasible. Participants were instructed to close their eyes while maintaining wakefulness for 9 min. Participants were asked to open their eyes every 3 min to prevent them from falling asleep. Prior to fitting the cap, the participant was asked to brush their hair to stimulate scalp blood flow. Acceptable impedances remained below 10 kΩ. EEG data were recorded with a sampling rate of 250 Hz. The participant sat about 60 cm in front of a 22-inch computer screen. The researcher used a second screen directly behind the participant to observe EEG data. The experiment was conducted in an evenly lit room, during either a morning or afternoon session.

6.2.3 EEG Analysis

Offline pre-processing of EEG data was done in EEGLAB (Delorme & Makeig, 2004; Delorme et al., 2011). EEG data were filtered from 1 Hz to 80 Hz and downsampled to 250 Hz. Prep pipeline was used to minimize line noise, identify bad electrodes, and re-reference to a common average of all electrodes (Bigdely-Shamlo et al., 2015). Large artefacts were minimised using ASR (Chang et al., 2020; Mullen et al., 2015), which was followed by an infomax ICA to remove stereotypical artefacts (Delorme et al., 2007). ICLabel and FASTER methods were used to identify artefactual components (Nolan et al., 2010; Pion-Tonachini et al., 2019). In addition, dipole fitting was performed and components with a corresponding current dipole outside the brain were removed. EEG data were then epoched into 2-s segments. Epoched data was inspected and noisy epochs were rejected. In addition, vertical oculogram (VEOG) was used to identify and reject epochs corresponding to eye blinks. For each participant, 90 epochs (i.e., 3 min) were randomly selected to avoid the confounding effect of number of epochs on estimation of spectral density. Fast fourier transform (FFT) with a Hanning window was applied to each epoch to estimate power spectral density, which were then averaged across all epochs.

Participants (N = 5) were excluded from analysis if more than 10 electrodes were identified as “noisy” (had an impedance of greater than 10 kΩ). A further 19 participants were visually excluded from the analysis. We calculated relative spectral powers in the following frequency ranges (Hz): 0.5-4 (delta), 4-8 (theta), 8-12 (alpha), and 13-29 (beta). Relative power was calculated by dividing the absolute power in each frequency band by the total power and was assessed over electrode-defined regions. The regions were defined as Anterior, Central and Posterior regions (Figure 6.2). In addition, individual alpha frequency (IAF) was estimated as the frequency of peak power in the extended alpha band (5-14 Hz) from the posterior region (Moretti et al., 2011; Moretti et al., 2012).

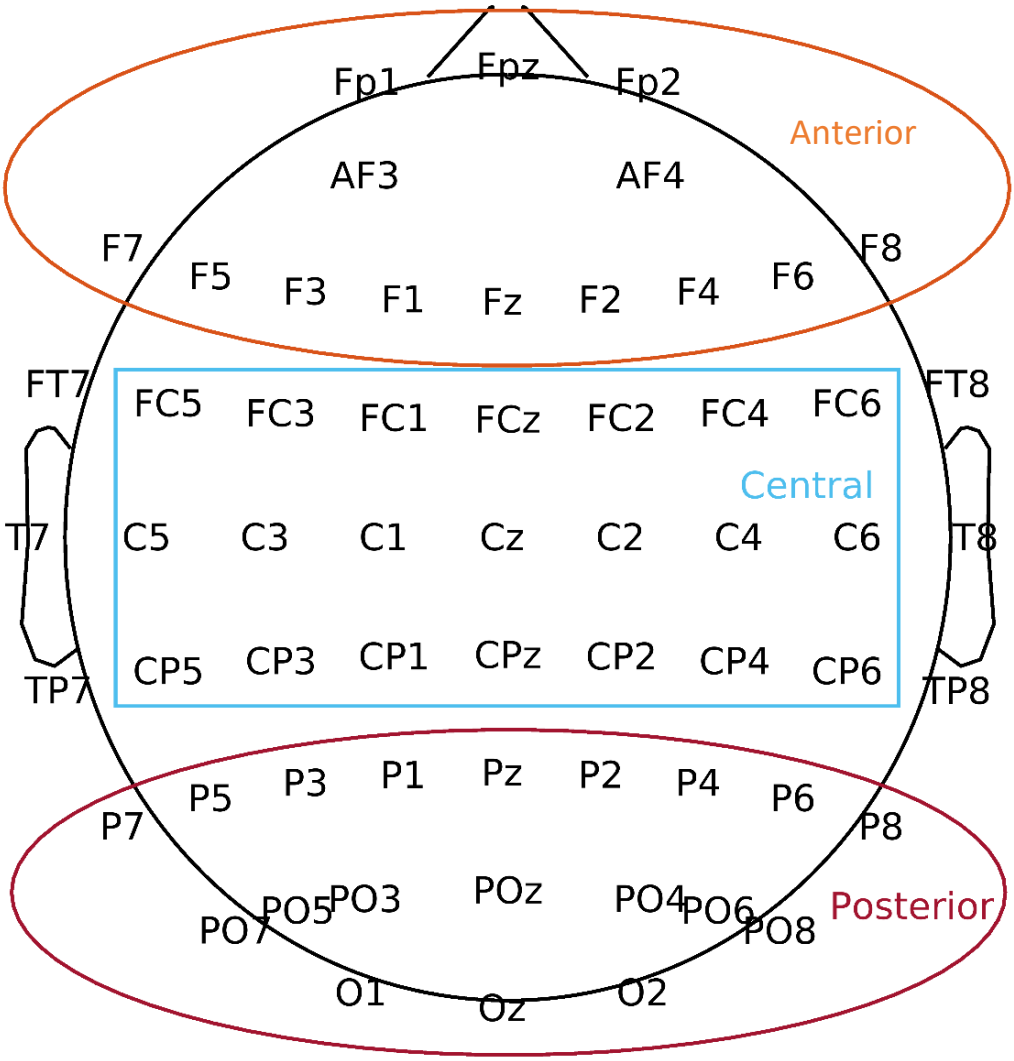

Figure 6.2 Three regions used to classify electrode clusters.

6.2.4 Statistical Analysis

R version 3.6.3 was used to conduct statistical analyses. IAF was compared across the four groups using a one-way ANCOVA with age and sex as covariates. The additional covariates of levodopa equivalent daily dosage (LEDD) and UPDRS-III were used when comparing PD groups only. As neither age, sex, LEDD nor UPDRS III covariates were statistically significant for IAF (all $F < 1.8$, $df = 1, 83$, all $p > 0.53$), or spectral power (all $F < 0.86$, $df = 1, 120$, all $p > 0.36$), and did not change the outcomes for other variables, the unadjusted model was used to show mean values for IAF and spectral power.

Spectral power in each of the four frequency bands for the four groups was analysed separately, using Group as the between-subject factor and Region as the repeated-measures factor. Any significant interaction of Group × Region was further explored by a post-hoc analysis. Tukey post-hoc comparisons determined pairwise differences between groups. As there were no significant main effects or interactions between the left and right hemisphere for any frequency band, the regions were analysed as a whole, as opposed to being separated into left and right sections.

6.3 Results

6.3.1 Participant Demographics and Group Characteristics

The PD and HC groups are described in Table 6.1. Detailed neuropsychological and neuropsychiatric measures in PDD participants are not provided in Table 6.1 for reasons given above, but PDD participants showed lower MoCA scores. Global Z scores are shown, based on the average z-scores across the "ten sensitive cognitive measures" used to define the PD-MCI group and, for comparison, the 21 neuropsychological tests used previously at the NZBRI to summarise cognition in patients with PD-MCI. The Global Z scores for the 21 tests were calculated by averaging each domain before computing an average of those scores. HC, PD-N, and PD-MCI groups differed on all neuropsychological tests. The two PD groups differed on all the neuropsychiatric measures also except the GDS. Whereas the Premorbid IQ scores were significantly different between all groups. There were no statistically significant differences between groups for

education. There were also significant differences between group means for the three PD groups for LEDD, although when used as covariate in the analysis it did not alter the EEG findings. The PD-N group was significantly younger than the other three groups. All confidence intervals are ±95%.

Table 6.1 Demographic, neuropsychological and neuropsychiatric measures for all participants with exclusions (mean ± SD).

Cognitive Group	HC	PD-N	PD-MCI	PDD	p < 0.05
N	29	44	40	12	
Male/Female	19/10	26/18	28/12	10/2	
Mean Age ± SD (years)	75.8±7.6	68.5±7.3	72.5±6.3	75.4±4.3	*
Symptom Duration ± SD (years)	-	9.7±5.6	12.9±6.5	13.8±5.4	*
LEDD	-	951±1126	995±531	1235±524	
Hoehn & Yahr Stage	-	2.2±0.5	2.6±0.5	2.7±0.4	*
UPDRS III	-	28.4±12.2	41.6±13	43±6.9	*
Education (years)	13.9±2.6	13.2±2.3	12.7±2.5	14.1±2.9	
Reisberg ADL	0.3±0.3	0.5±0.5	0.9±0.6	-	*
MoCA	26.6±2.3	26.9±2.3	23.6±2.4	18.5±4.9	*
Global Z 21 tests	0.82±0.44	0.29±0.42	-0.59±0.45	-	*
Global Z 10 tests	0.74±0.38	0.15±0.4	-0.95±0.54	-	*
Premorbid IQ (WTAR)	114.21±7.56	112.22±9.04	108.97	112.5±8.82	
GDS	-	0.05±0.21	0.23±0.48	-	
NPI	-	5.48±6.49	6.2±3.72	15±14.47	*
Executive Function					
Stroop Interference	**0.83±0.62**	**0.39±0.88**	**-0.72±1.32**	-	*
Trails B	**0.91±0.71**	**0.51±0.58**	**-1.07±1.43**	-	*
Action (verb) Fluency	0.29±1.01	-0.37±1.1	-1.07±1.12	-	*
Letter Fluency	1.37±1.27	0.87±1.26	0.21±1.13	-	*
Category Fluency	1.59±1.09	1.02±0.94	0.01±0.99	-	*
Category Switching	0.77±1.09	0.19±0.94	-0.81±0.99	-	*
Attention					
Digit Ordering	**0.27±1.57**	**-0.36±1.09**	**-1.36±1.1**	-	*
Map Search 1min	**0.44±0.89**	**-0.4±0.91**	**-1.59±0.88**	-	*
Stroop Word Reading	0.47±0.61	0.1±1.03	-0.53±0.8	-	*
Stroop Colour Naming	0.28±0.91	-0.251.09	-0.77±0.85	-	*
Digits Forward & Back	0.99±1.20	0.58±1.06	-0.13±0.78	-	*
Trails A	1.07±0.60	0.56±0.56	-0.21±1.03	-	*
Episodic Memory					
CVLT II Immediate Recall	**1.87±0.90**	**0.91±1.12**	**-0.35±1.29**	-	*
Rey Immediate Recall	**1.62±1.21**	**0.66±1.19**	**-0.68±1.38**	-	*
CVLT II Long Delay	0.96±0.94	0.33±0.86	-0.07±0.91	-	*
Visuoperceptual					
Rey Copy	**-0.12±0.76**	**-0.25±0.94**	**-1.97±1.04**	-	*
Judgement of Line	**0.37±0.72**	**0.25±0.66**	**-0.73±1.07**	-	*
VOSP Fragmented Letters	0.49±0.67	0.45±0.71	-0.12±0.98	-	*
Language					
Mattis DRS-2: Similarities	**0.33±0.00**	**-0.06±0.69**	**-0.41±0.89**	-	*
ADAS-Cog: Language	**0.1±0.63**	**-0.12±0.6**	**-0.66±0.84**	-	*

All pairwise comparisons are different (except sex, LEDD, education, WTAR and GDS). Bolded text indicates the ten neuropsychological tests used in Myall et al. (2020) for cognition. Cognitive measures are z-scores. Abbreviations: ADAS = Alzheimer's Disease Assessment Scale; ADL = Activities of Daily Living; CVLT = California Verbal Learning Test; DRS = Dementia Rating Scale; HC = HC; MoCA = Montreal Cognitive Assessment; NA = Not Applicable; PD-N = Participants with PD who have relatively normal cognition (i.e. do not meet the criteria for PD-MCI); PD-MCI = PD with mild cognitive impairment; PDD = PD with dementia; SD = Standard Deviation; UPDRS = Unified Parkinson's Disease Rating Scale; VOSP = Visuospatial Object and Space Perception; WTAR = Wechsler Test of Adult Reading

6.3.2 Individual Alpha Frequency

Alpha power is observed primarily in the posterior region of the brain during eyes-closed resting wakefulness. Figure 6.3 displays the correlation for the Anterior, Central, and Posterior region to outline the strong positive correlation across all regions (all r > 0.77). The three regions were reported for observation, although the strongest correlation was seen between IAF in the posterior region. For the remainder of the chapter, IAF was derived from the posterior electrodes only.

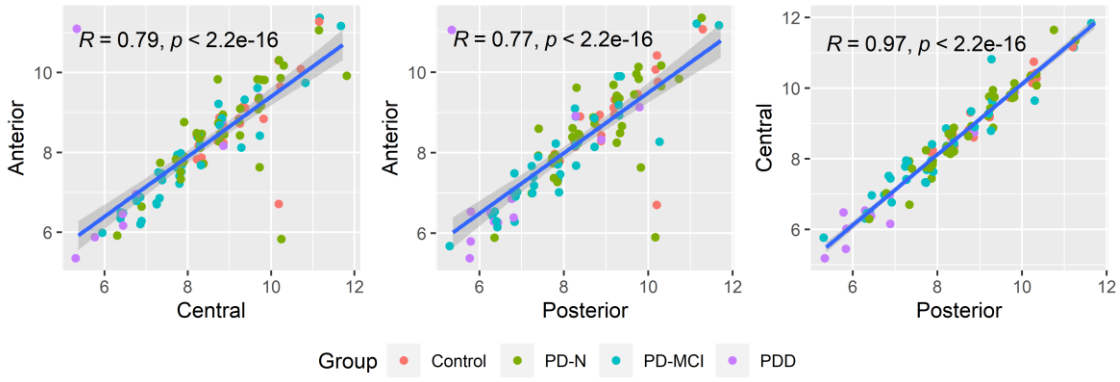

Figure 6.3 Scattergram of IAF for all groups, across all regions.

The mean individual alpha frequency for the four groups is shown in Figure 6.4. The mean IAF was highest in the HC group and progressively decreased across PD-N, PD-MCI and PDD groups (Group, $F(3,121) = 12.26$, $p < 0.01$). Significant post-hoc Tukey comparisons were evident for all pairwise comparisons, except HC versus PD-N groups (Table 6.2). The IAF values produced very large Cohen d effect sizes between both HC and PDD groups and between PD-N and PDD groups ($d = 1.83$ and $d = 1.52$, respectively). Large effect sizes were evident between both PD-MCI and HC groups, and PD-MCI and PDD groups ($d = 0.93$ and $d = 0.90$, respectively). Small and medium effect sizes, respectively, were found between PD-N and HC groups and PD-N and PD-MCI groups (Table 6.2). This pattern suggests that the IAF remains relatively stable in PD-N, but declines substantially, on average, once patients meet the PD-MCI criteria used in this study, and especially once they meet criteria for PDD.

When IAF values were examined only in the PD groups and adjusted using UP-DRS-III (motor scores), L-Dopa equivalent, and age as covariates, the PD-N versus PD-MCI pairwise difference was no longer significant ($p > 0.18$), but the PD-N versus PDD and PD-MCI versus PDD differences remained significant ($p < 0.001$ and $p < 0.03$, respectively); the corresponding effect sizes remained similar ($d = 1.33$ and $d = 0.88$, respectively).

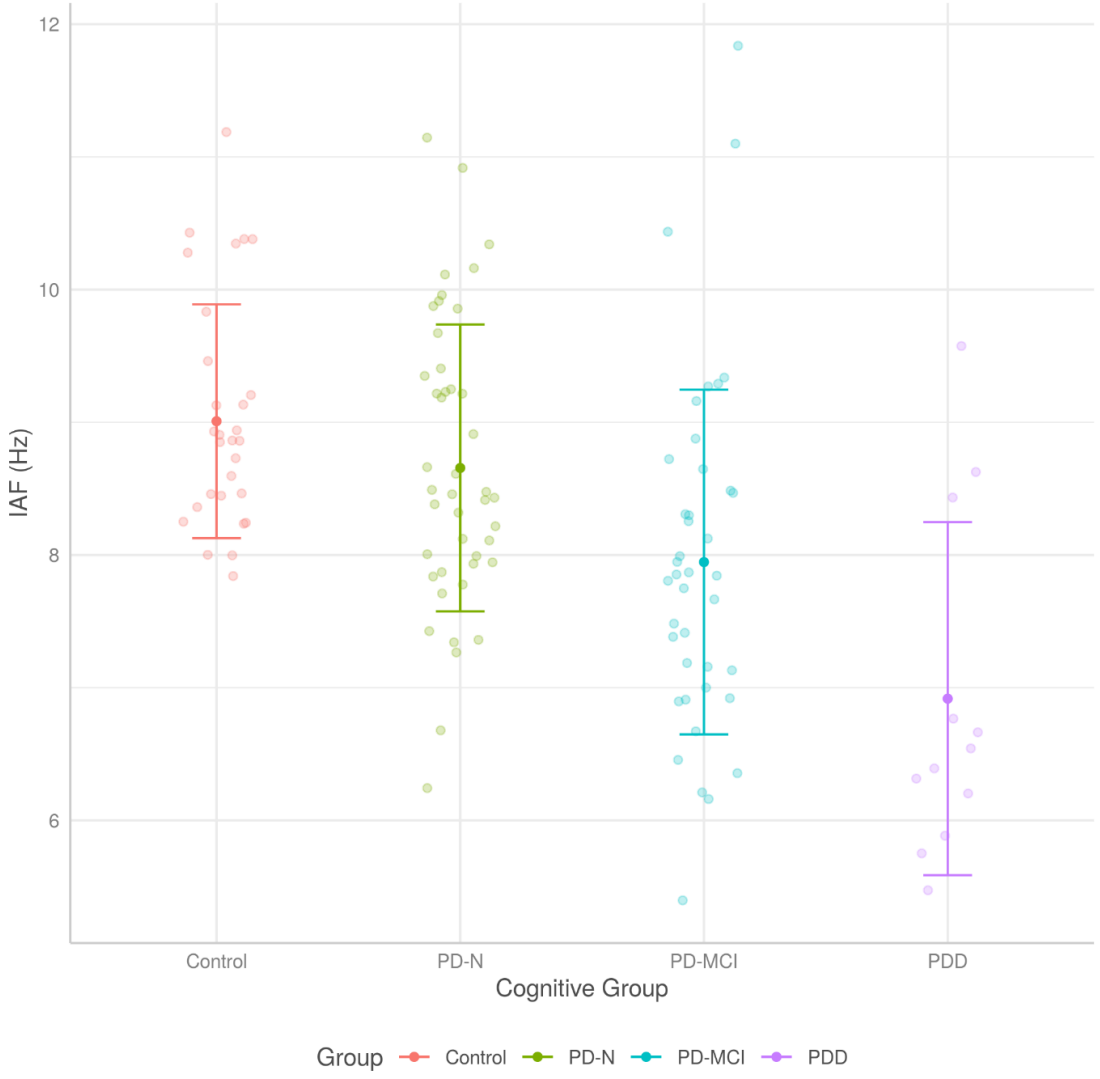

Figure 6.4 Mean IAF ± SD for the four groups with corresponding individual values.

Table 6.2 IAF: Group comparisons.

Group	Difference (SE)	t value	p value	Effect Size (±95%CI)	
				Unadjusted	Adjusted for age, UPDRS III and LEDD
HC - PD-N	0.35 (0.27)	1.3	0.570	0.30 (-0.17, 0.78)	-
HC - PD-MCI	1.06 (0.28)	3.8	0.001	0.93 (0.41, 1.40)	-
HC - PDD	2.09 (0.39)	5.3	0.000	1.83 (1.06, 2.60)	-
PD-N - PD-MCI	0.71 (0.25)	2.8	0.026	0.62 (0.17, 1.07)	0.45 (-0.06, 0.97)
PD-N - PDD	1.74 (0.37)	4.7	0.000	1.52 (0.81, 2.23)	1.33 (0.56, 2.1)
PD-MCI - PDD	1.03 (0.38)	2.7	0.035	0.90 (0.22, 1.57)	0.88 (0.18, 1.57)

Adjusted for multiple comparisons with Tukey. Difference values are measures in Hz.
Abbreviations: Participants with PD who have relatively normal cognition (i.e. do not meet the criteria for PD-MCI); PD-MCI = PD with mild cognitive impairment; PDD = PD with dementia

The relationship between the average cognitive Z-score (across the 10 tests) and IAF is shown in Figure 6.5. There was a significant correlation between IAF and global z score for the 10 cognitive tests. IAF declined as cognition declined for all regions ($r = 0.36$, $p < 0.001$).

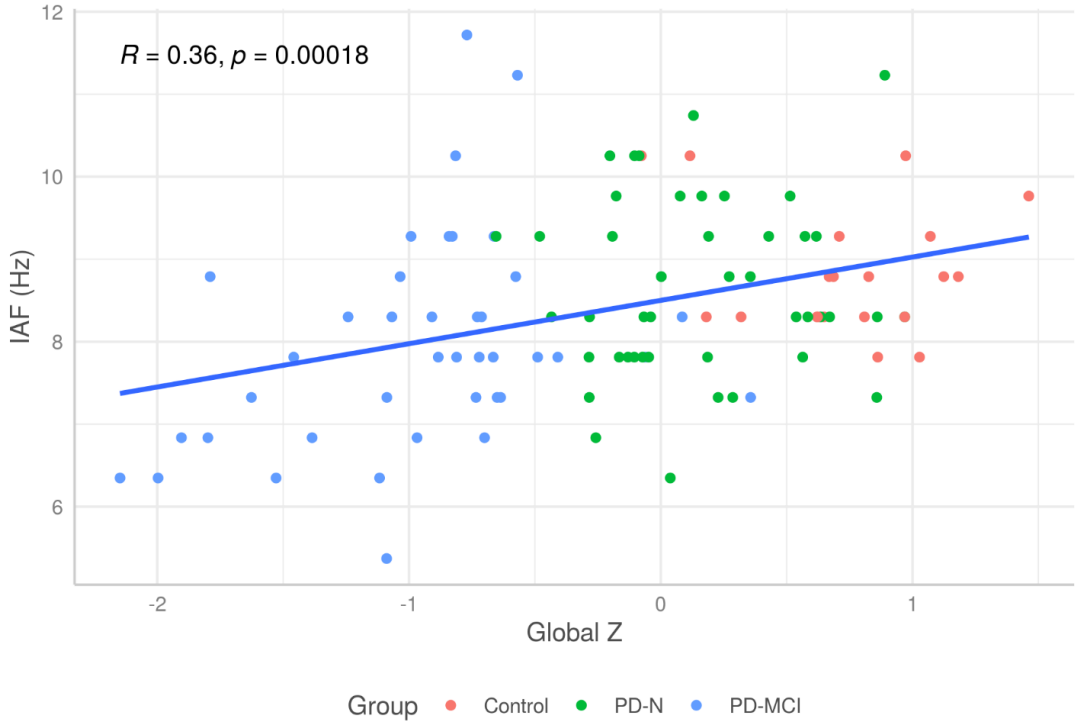

Figure 6.5 Scattergram of the IAF with aggregate Z-score for the ten neuropsychological measures, for all groups.

6.3.3 Spectral Power analysis

Spectral power differences between groups were particularly evident in the theta and alpha bands (Figure 6.6). All bands produced significant main effects for Electrode Region (All $F > 17.13$, $df = 2, 242$, all $p < 0.001$), but there were also significant Group × Region interactions for all bands (all $F > 2.58$, $df = 6, 242$, $p < 0.02$). The Group × Region interactions were followed up with simple main effects analyses and post-hoc pairwise comparisons. The conclusions remained the same when age and sex were included as covariates.

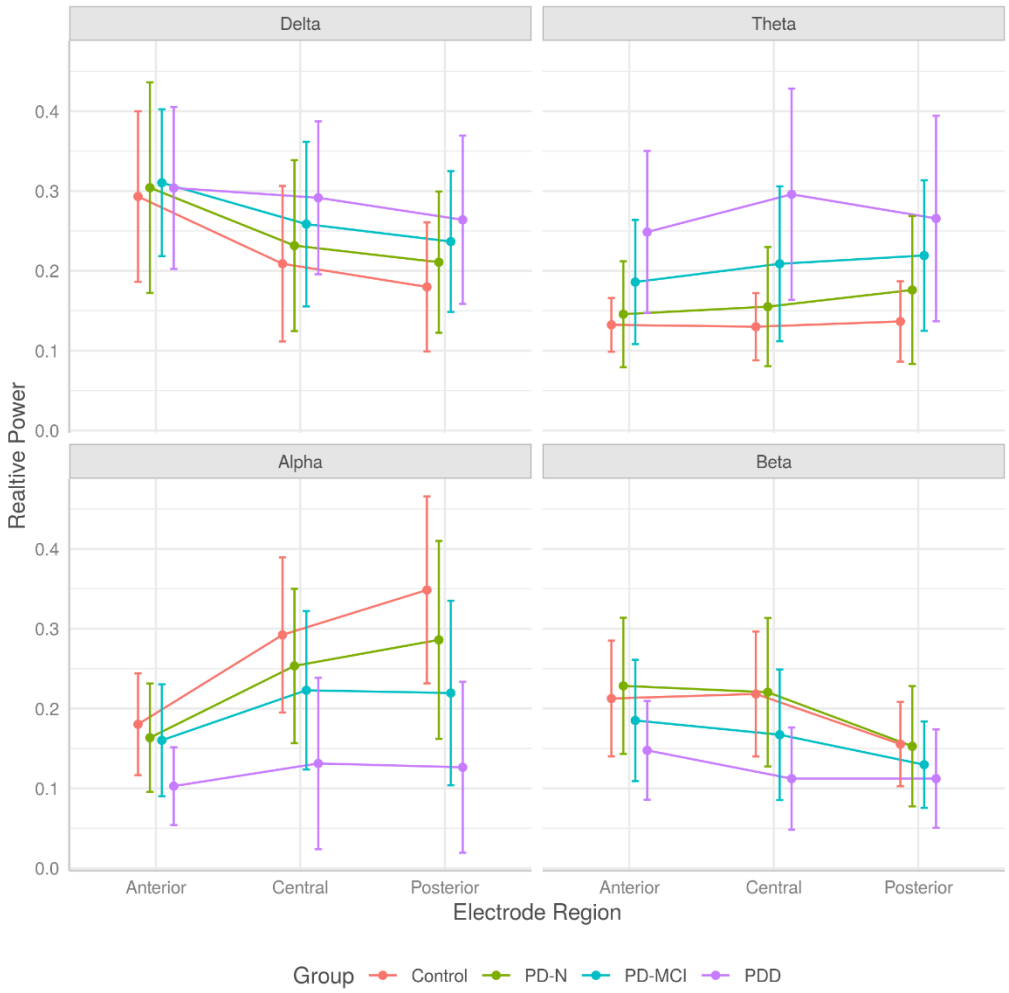

Figure 6.6 Mean spectral power ± SD for four frequency bands in the four groups, across the three electrode regions.

There was no significant main effect of Group ($F(3, 120) = 1.62$, $p = 0.18$) for the delta band. The HC, PD-N, and PD-MCI groups showed a reduction in delta power

across frontal to central and then to posterior electrode regions, but this was not apparent in the PDD group. Post-hoc analysis of the Group × Region interaction confirmed a simple main effect of Region for the HC, PD-N and PD-MCI groups ($p < 0.001$); and no regional decline for the PDD group ($p = 0.12$). The groups showed similar power in the Anterior Region (simple main effect of Group, $F(3, 158) = 0.14$, $p = 0.93$). While the simple main effect of Group was close to significance for the Central Region of electrodes ($F(3, 158) = 2.47$, $p = 0.06$) and the Posterior Region ($F(3,119) = 2.68$, $p = 0.05$), neither region showed any pairwise group differences (Table 6.3). The most reliable effect sizes were between HCs and the PDD group for the central ($d = -1.70$, CI = -3.15, -0.24) and posterior regions ($d = -1.72$, CI = -3.17, -0.27) and between HCs and PD-MCI for the posterior region ($d = -1.15$, CI = -2.19, -0.11). This pattern suggests that the primary differences were higher delta power in the central and posterior regions for the PDD group relative to the HC group, and higher delta power in the posterior region for the PD-MCI group.

For the theta band, the PD-N, PD-MCI, and PDD groups showed changes in power across Region, but not for the HC group. There was a significant main effect of Group ($F(3, 120) = 11.41$, $p < 0.001$) with higher mean theta power in the PDD group and to a lesser degree in the PD-MCI group. Analysis of the Group by Region interaction confirmed a simple main effect of Region for the PD-N, PD-MCI and PDD groups ($p < 0.002$); there was no regional difference for the HC group, $p = 0.74$. Post-hoc comparisons confirmed a significant main effect of Group in the Anterior Region of electrodes, ($F(3, 145) = 7.23$, $p < 0.001$), Central Region of electrodes ($F(3, 145) = 14.53$, $p < 0.001$), and Posterior Region of electrodes ($F(3, 145) = 9.86$, $p < 0.001$). In the Anterior Region there were significant pairwise differences between the HC and PDD groups, as well as between the PD-N and PDD groups higher theta power in the PDD group. In the Central Region there were significant pairwise differences between all groups except between the HC and PD-N group. In the Posterior Region there were significant pairwise differences between the HC group and both the PD-MCI and PDD group, as well as between the PD-N and PDD groups (Table 6.4). The large reliable effect sizes were found between HCs and the PDD groups, between the HC and the PD-MCI groups for all regions and between the PD-N and PDD groups across regions (Table 6.4).

Table 6.3 Delta band spectral power differences in the four groups.

Cognitive Group	Region	Difference	t ratio	p value	Effect size (±95%CI)
HC - PD-N	Anterior	-0.01	-0.36	0.983	-0.19 (-1.25, 0.86)
HC - PD-MCI	Anterior	-0.02	-0.66	0.914	-0.34 (-1.36, 0.68)
HC - PDD	Anterior	-0.01	-0.30	0.990	-0.22 (-1.63, 1.20)
PD-N - PD-MCI	Anterior	-0.01	-0.31	0.990	-0.14 (-1.07, 0.78)
PD-N - PDD	Anterior	0.00	-0.03	1.000	-0.02 (-1.41, 1.36)
PD-MCI - PDD	Anterior	0.01	0.17	0.998	0.12 (-1.24, 1.49)
HC - PD-N	Central	-0.02	-0.82	0.845	-0.44 (-1.49, 0.62)
HC - PD-MCI	Central	-0.05	-1.95	0.212	-1.01 (-2.04, 0.03)
HC - PDD	Central	-0.08	-2.37	0.088	-1.70 (-3.15, -0.24)
PD-N - PD-MCI	Central	-0.03	-1.22	0.617	-0.57 (-1.50, 0.36)
PD-N - PDD	Central	-0.06	-1.79	0.281	-1.26 (-2.67, 0.15)
PD-MCI - PDD	Central	-0.03	-1.00	0.751	-0.69 (-2.06, 0.68)
HC - PD-N	Posterior	-0.03	-1.13	0.670	-0.60 (-1.66, 0.47)
HC - PD-MCI	Posterior	-0.06	-2.23	0.119	-1.15 (-2.20, -0.11)
HC - PDD	Posterior	-0.08	-2.41	0.080	-1.72 (-3.18, -0.27)
PD-N - PD-MCI	Posterior	-0.03	-1.17	0.645	-0.55 (-1.48, 0.38)
PD-N - PDD	Posterior	-0.05	-1.59	0.384	-1.12 (-2.52, 0.28)
PD-MCI - PDD	Posterior	-0.03	-0.83	0.841	-0.57 (-1.94, 0.80)

Abbreviations: PD-N = Participants with PD who have relatively normal cognition (i.e. do not meet the criteria for PD-MCI); PD-MCI = PD with mild cognitive impairment; PDD = PD with dementia; C.I = Confidence interval

Table 6.4 Theta band spectral power differences in the four groups.

Cognitive Group	Region	Difference	t ratio	p value	Effect size (±95%CI)
HC - PD-N	Anterior	-0.02	-0.97	0.766	-0.62 (-1.89, 0.65)
HC - PD-MCI	Anterior	-0.06	-2.83	0.027	-1.74 (-3.00, -0.48)
HC - PDD	Anterior	-0.12	-4.19	0.000	-3.58 (-5.41, -1.75)
PD-N - PD-MCI	Anterior	-0.04	-2.01	0.190	-1.12 (-2.25, 0.01)
PD-N - PDD	Anterior	-0.10	-3.53	0.003	-2.96 (-4.72, -1.20)
PD-MCI - PDD	Anterior	-0.06	-2.23	0.120	-1.84 (-3.51, -0.17)
HC - PD-N	Central	-0.03	-1.54	0.416	-0.98 (-2.26, 0.29)
HC - PD-MCI	Central	-0.08	-4.08	0.000	-2.51 (-3.83, -1.20)
HC - PDD	Central	-0.17	-5.97	0.000	-5.10 (-7.07, -3.14)
PD-N - PD-MCI	Central	-0.05	-2.74	0.035	-1.53 (-2.67, 0.39)
PD-N - PDD	Central	-0.13	-4.91	0.000	-4.12 (-5.97, -2.27)
PD-MCI - PDD	Central	-0.08	-3.14	0.011	-2.59 (-4.30, -0.88)
HC - PD-N	Posterior	-0.05	-2.23	0.120	-1.42 (-2.71, -0.13)
HC - PD-MCI	Posterior	-0.09	-4.27	0.000	-2.63 (-3.95, -1.31)
HC - PDD	Posterior	-0.13	-4.65	0.000	-3.97 (-5.83, -2.11)
PD-N - PD-MCI	Posterior	-0.04	-2.17	0.138	-1.21 (-2.34, -0.08)
PD-N - PDD	Posterior	-0.08	-3.04	0.015	-2.55 (-4.28, -0.82)
PD-MCI - PDD	Posterior	-0.04	-1.63	0.367	-1.34 (-2.99, 0.31)

Abbreviations: PD-N = Participants with PD who have relatively normal cognition (i.e. do not meet the criteria for PD-MCI); PD-MCI = PD with mild cognitive impairment; PDD = PD with dementia; C.I = Confidence interval

There was a significant main effect of Group ($F(3, 120) = 10.04$, $p < 0.001$) for the alpha band. The HC, PD-N and PD-MCI groups showed an increase in power across frontal to posterior electrode regions, but this was not apparent in the PDD group. Analysis of the Group by Region interaction confirmed a main effect of Region for the HC, PD-N and PD-MCI groups ($p < 0.001$) but no regional increase for the PDD group ($p = 0.37$). The groups showed similar power in the Anterior region (main effect of Group, $F(3, 173) = 1.82$, $p = 0.14$). There was a significant main effect of Group for both the central region, $F(3,173) = 8.51$, $p < 0.001$, and the posterior region, $F(3,173) = 19.02$, $p < 0.001$. In the Central region, there were significant pairwise differences between all groups except the HC and PD-N group and the PD-N and PD-MCI group. In the Posterior region, however, there were significant pairwise differences for all pairwise group comparisons, even HC vs PD-N, with all $d > 1.0$ (Table 6.5). Very large effect sizes were found between HC and the PDD group for the central ($d = 3.04$, CI = 1.67, 4.41) and posterior regions ($d = 4.19$, CI = 2.70, 5.68) and between HC and PD-MCI for the posterior region ($d = 2.49$, CI = 1.48, 3.51). That is, the clearest effects for alpha power

between HC and the PD groups occurred in the Posterior (electrode) Region, but this region also produced large effect sizes for all comparisons of cognitive status in PD.

There was also a significant main effect of Group ($F(3, 120) = 4.97$, $p < 0.01$) for the beta band. The PD-MCI and PDD groups showed a reduction in power across the frontal to central region, but this was not apparent in the HC and PD-N groups. The HC, PD-N and PD-MCI groups also showed a reduction in power across the central to posterior region, but this was not seen in the PDD group. Analysis of the Group by Region interaction confirmed a main effect of Region for all four groups ($p < 0.05$). The groups showed similar power in the Posterior region (main effect of Group, $F(3,159) = 1.48$, $p = 0.22$). There was a main effect of Group within the anterior region, $F(3,159) = 4.18$, $p < 0.01$, and the central region, $F(3,159) = 8.66$, $p < 0.001$. In the Anterior region, there were significant pairwise differences between the PD-N and PDD group. In the Central region there were significant pairwise differences between all groups except the HC and PD-N group and the PD-MCI and PDD group (Table 6.6). Very large effect sizes were found between the HC and the PDD group for the central region ($d = 2.91$, CI = 1.40, 4.42) and between the PD-N and PDD groups for the anterior ($d = 2.09$, CI = 0.66, 3.52) and central regions ($d = 2.84$, CI = 1.36, 4.32). The PD-MCI and PDD groups only differed in the central region ($d = 1.46$, CI = 0.08, 2.84).

Table 6.5 Alpha band spectral power differences in the four groups.

Cognitive Group	Region	Difference	t ratio	p value	Effect size (±95%CI)
HC - PD-N	Anterior	0.02	0.99	0.753	0.46 (-0.46, 1.38)
HC - PD-MCI	Anterior	0.02	0.98	0.760	0.44 (-0.45, 1.34)
HC - PDD	Anterior	0.08	2.34	0.093	1.47 (0.20, 2.74)
PD-N - PD-MCI	Anterior	0.00	-0.05	1.000	-0.02 (-0.83, 0.79)
PD-N - PDD	Anterior	0.05	1.64	0.359	1.01 (-0.22, 2.23)
PD-MCI - PDD	Anterior	0.05	1.70	0.329	1.03 (-0.18, 2.23)
HC - PD-N	Central	0.05	1.89	0.235	0.88 (-0.05, 1.81)
HC - PD-MCI	Central	0.07	3.05	0.014	1.37 (0.43, 2.30)
HC - PDD	Central	0.16	4.86	0.000	3.05 (1.67, 4.42)
PD-N - PD-MCI	Central	0.03	1.21	0.620	0.50 (-0.32, 1.31)
PD-N - PDD	Central	0.11	3.53	0.003	2.17 (0.88, 3.45)
PD-MCI - PDD	Central	0.09	2.77	0.031	1.67 (0.44, 2.91)
HC - PD-N	Posterior	0.07	2.85	0.025	1.32 (0.37, 2.23)
HC - PD-MCI	Posterior	0.13	5.54	0.000	2.50 (1.48, 3.52)
HC - PDD	Posterior	0.22	6.70	0.000	4.20 (2.71, 5.68)
PD-N - PD-MCI	Posterior	0.06	2.88	0.023	1.18 (0.34, 2.01)
PD-N - PDD	Posterior	0.15	4.68	0.000	2.87 (1.54, 4.21)
PD-MCI - PDD	Posterior	0.09	2.81	0.028	1.70 (0.46, 2.94)

Abbreviations: PD-N = Participants with PD who have relatively normal cognition (i.e. do not meet the criteria for PD-MCI); PD-MCI = PD with mild cognitive impairment; PDD = PD with dementia; C.I = Confidence interval

Table 6.6 Beta band spectral power differences in the four groups.

Cognitive Group	Region	Difference	t ratio	p value	Effect size (±95%CI)
HC - PD-N	Anterior	-0.01	-0.58	0.937	-0.31 (-1.35, 0.73)
HC - PD-MCI	Anterior	0.03	1.59	0.389	0.81 (-0.21, 1.83)
HC - PDD	Anterior	0.07	2.52	0.060	1.79 (0.34, 3.23)
PD-N - PD-MCI	Anterior	0.04	2.42	0.078	1.12 (0.18, 2.06)
PD-N - PDD	Anterior	0.08	3.02	0.016	2.09 (0.66, 3.53)
PD-MCI - PDD	Anterior	0.04	1.43	0.483	0.98 (-0.39, 2.34)
HC - PD-N	Central	0.00	0.13	0.999	0.07 (-0.97, 1.11)
HC - PD-MCI	Central	0.05	2.85	0.025	1.46 (0.41, 2.50)
HC - PDD	Central	0.11	4.11	0.000	2.91 (1.40, 4.43)
PD-N - PD-MCI	Central	0.05	3.00	0.016	1.39 (0.43, 2.34)
PD-N - PDD	Central	0.10	4.10	0.000	2.84 (1.36, 4.33)
PD-MCI - PDD	Central	0.05	2.13	0.147	1.46 (0.08, 2.84)
HC - PD-N	Posterior	0.01	0.38	0.981	0.20 (-0.84, 1.24)
HC - PD-MCI	Posterior	0.03	1.50	0.442	0.76 (-0.26, 1.78)
HC - PDD	Posterior	0.04	1.68	0.336	1.19 (-0.23, 2.61)
PD-N - PD-MCI	Posterior	0.02	1.22	0.616	0.56 (-0.36, 1.48)
PD-N - PDD	Posterior	0.04	1.43	0.484	0.99 (-0.39, 2.38)
PD-MCI - PDD	Posterior	0.02	0.63	0.923	0.43 (-0.92, 1.78)

Abbreviations: PD-N = Participants with PD who have relatively normal cognition (i.e. do not meet the criteria for PD-MCI); PD-MCI = PD with mild cognitive impairment; PDD = PD with dementia; C.I = Confidence interval

Alpha had the largest main effect of group and hence was chosen to investigate its association with global Z score (average across 10 tests). Since there was no evidence of an interaction between group and region, the connectivity measures were taken from the posterior region as this region showed the most significant differences between groups. The relationship between the average cognitive Z-score (across the 10 tests) and alpha spectral power for the posterior region is shown in Figure 6.7. The posterior region showed a significant correlation between alpha spectral power and global z score for the 10 cognitive tests. Alpha spectral power in the posterior region declined as cognition declined for all regions ($r = 0.44$, $p < 0.001$).

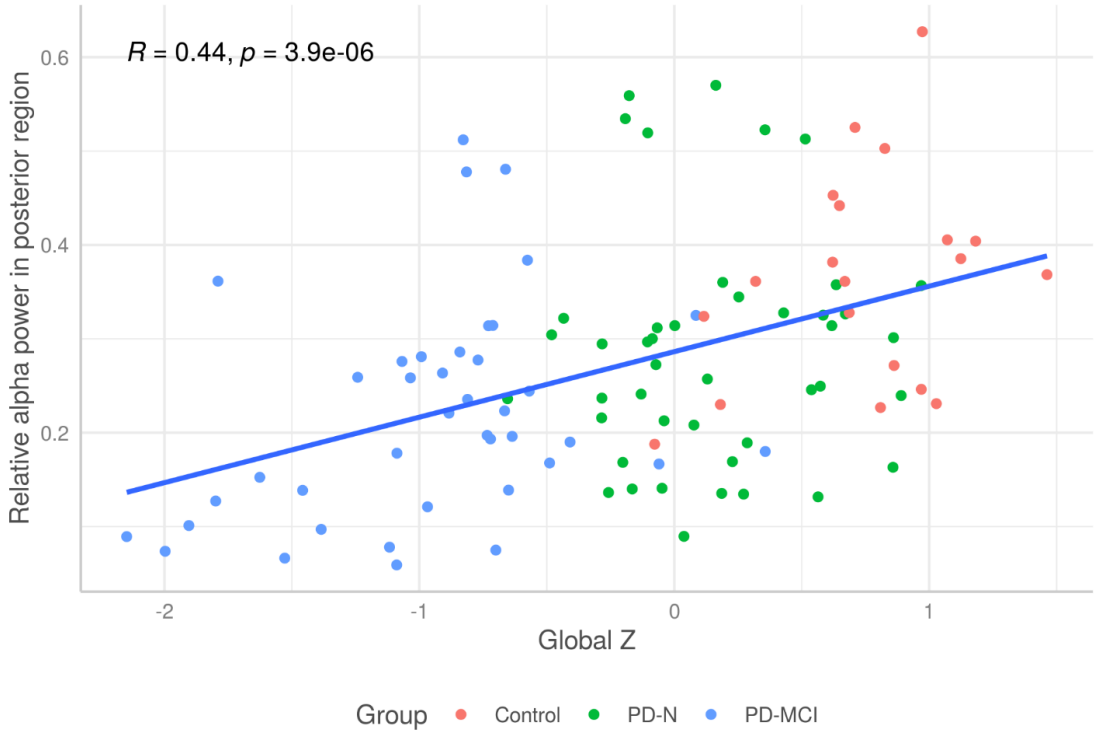

Figure 6.7 Scattergram of Spectral power for the Alpha band in the posterior region with aggregate Z-score for the ten neuropsychological measures, for all groups.

6.4 Theta/Alpha Band Ratio

The theta/alpha ratio provides a within-subject measure that controls for variation across subjects in terms of relative power. There was a significant main effect of Region ($F(3, 362) = 8.83$, $p < 0.001$) and Group ($F(3, 362) = 47.47$, $p < 0.001$), with the

PDD group showing an elevated ratio by comparison to HC (Figure 6.8). Analysis of Group by Region interaction confirmed a main effect of Region for the HC and PD-N groups ($p < 0.01$); there were no regional differences for the PD-MCI ($p = 0.41$) or PDD groups ($p = 0.98$). There was a significant main effect of Group within the Anterior Region, $F(3,362) = 8.22$, $p < 0.001$, Central Region, $F(3, 362) = 18.99$, $p < 0.001$, and the Posterior Region, $F(3,362) = 22.88$, $p < 0.001$. In the Anterior region, the PDD group was significantly different to all the other three groups which did not differ. In the Central Region, there were significant pairwise differences between all groups except the HC and PD-N group. In the Posterior Region, however, there were significant differences for all pairwise group comparisons, even HC vs PD-N, with all $d < -0.65$ (Table 6.7). Large effect sizes were found between HC and the PDD group for the central region ($d = -2.41$, CI = -3.24, -1.59) and posterior region ($d = -2.53$, CI = -3.37, -1.69) and between PD-N and PDD for the central region ($d = -1.97$, CI = -2.72, -1.21) and posterior region ($d = -1.88$, CI = -2.63, -1.13). Medium effect sizes between the PD-N and PD-MCI groups were evident for the central and posterior regions, but larger differences were evident between PD-MCI and PDD groups for these regions (Table 6.7).

The relationship between the average cognitive Z-score (across the 10 tests) and spectral power Theta/Alpha ratio for all regions is shown in Figure 6.9. The log values were used to correct for non-normality. All regions showed a significant correlation between theta/alpha spectral power ration and global Z score for the 10 cognitive tests. Spectral power ratio increased as cognition declined for all regions, and this was strongest in the posterior region ($r = -0.45$).

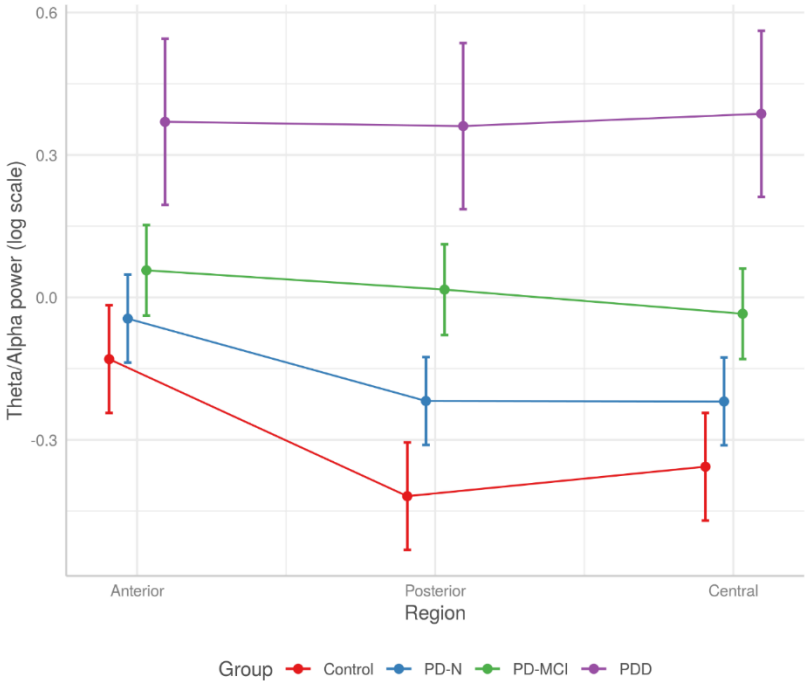

Figure 6.8 Mean spectral power ± SD for the Theta/Alpha ratio in the four groups, across the three electrode regions.

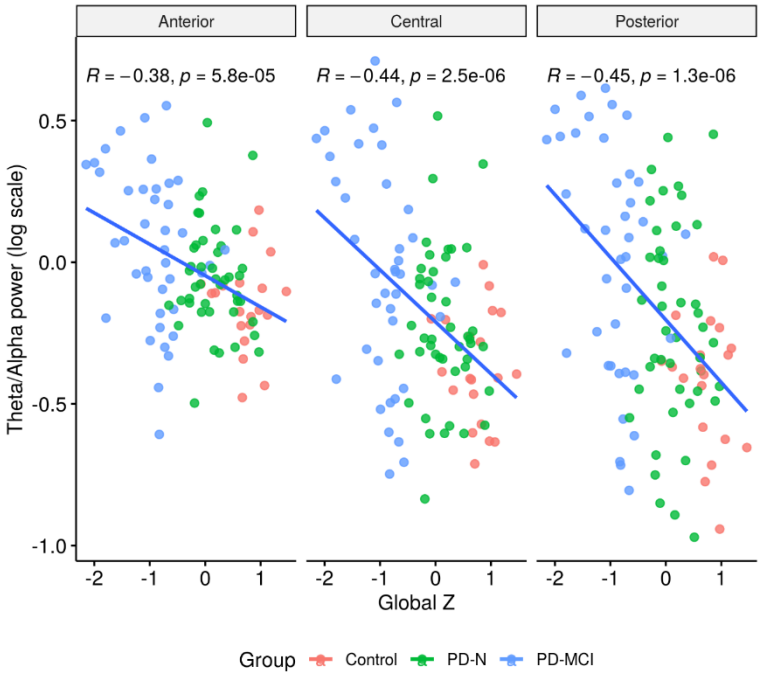

Figure 6.9 Scattergram of Spectral power for the Theta/Alpha ratio (log_{10}) with aggregate Z-score for the ten neuropsychological measures, for all groups, for all regions.

Table 6.7 Ratio for the Theta/Alpha band spectral power differences in the four groups.

Cognitive Group	Region	Difference	t ratio	p value	Effect size (±95%CI)
HC - PD-N	Anterior	-0.09	-1.1	0.673	-0.28 (-0.76, 0.21)
HC - PD-MCI	Anterior	-0.19	-2.5	0.065	-0.61 (-1.10, -0.11)
HC - PDD	Anterior	-0.50	-4.7	0.000	-1.62 (-2.37, -0.88)
PD-N - PD-MCI	Anterior	-0.10	-1.5	0.440	-0.33 (-0.77, 0.11)
PD-N - PDD	Anterior	-0.41	-4.1	0.000	-1.35 (-2.05, -0.65)
PD-MCI - PDD	Anterior	-0.31	-3.1	0.012	-1.02 (-1.70, -0.34)
HC - PD-N	Central	-0.14	-1.8	0.267	-0.45 (-0.94, 0.05)
HC - PD-MCI	Central	-0.32	-4.3	0.000	-1.05 (-1.57, -0.52)
HC - PDD	Central	-0.74	-7.0	0.000	-2.41 (-3.24, -1.59)
PD-N - PD-MCI	Central	-0.18	-2.7	0.034	-0.60 (-1.05, -0.15)
PD-N - PDD	Central	-0.61	-6.0	0.000	-1.97 (-2.72, -1.21)
PD-MCI - PDD	Central	-0.42	-4.1	0.000	-1.37 (-2.07, -0.67)
HC - PD-N	Posterior	-0.20	-2.7	0.041	-0.65 (-1.15, -0.15)
HC - PD-MCI	Posterior	-0.44	-5.8	0.000	-1.41 (-1.97, -0.86)
HC - PDD	Posterior	-0.78	-7.4	0.000	-2.53 (-3.37, -1.69)
PD-N - PD-MCI	Posterior	-0.23	-3.5	0.003	-0.76 (-1.22, -0.30)
PD-N - PDD	Posterior	-0.58	-5.7	0.000	-1.88 (-2.63, -1.13)
PD-MCI - PDD	Posterior	-0.34	-3.4	0.004	-1.12 (-1.80, -0.43)

Abbreviations: PD-N = Participants with PD who have relatively normal cognition (i.e. do not meet the criteria for PD-MCI); PD-MCI = PD with mild cognitive impairment; PDD = PD with dementia; C.I = Confidence interval

6.5 Discussion

The main findings from this study was that the IAF remains relatively stable in PD-N, but declines substantially, on average, once patients met the PD-MCI criteria used in this study, and especially once they met criteria for PDD. Spectral power differences were most evident in the alpha and theta band. On average across region in the theta band, spectral power was the highest in the PDD group. However spectral power declined substantially once patients met the criteria for PD-MCI, and especially when they were classified as PD-N or HC. In the alpha band, posterior spectral power was highest in the HC group and declined across groups from the PD-N, to the PD-MCI and lastly to the PDD group. There was a main effect of region for theta/alpha ratio with the PDD group showing an elevated ratio by comparison to the HC group.

These cross-sectional findings are consistent with other studies that have looked at the spectral power differences in PD. Both our study and previous studies have found that PD-MCI and PDD patients report an increase in spectral power primarily in the

theta band and a reduction in spectral power in the alpha band compared to HCs and non-demented PD groups (Caviness et al., 2016; Chaturvedi et al., 2019; Fonseca et al., 2013; Fonseca et al., 2009; Ponsen et al., 2012), although, only two previous have made a direct comparison between a HC, PD-N, PD-MCI, and PDD group (Caviness et al., 2016; Fonseca et al., 2009). Despite the similar findings to the previous literature, our study used a criterion developed by Myall et al. (2020), for classifying cognition that has been shown to better identify patients who are at increased risk of progression to PDD which strengthens the findings of our study.

Our IAF findings are also consistent with another study which reported IAF decreases as cognition declines (Babiloni et al., 2017a). Thus, patients with PD who are cognitively impaired have lower IAF and increased theta relative spectral power. The PDD group had significantly lower IAF than the PD-N group. These IAF findings extend prior literature as no previous study has investigated IAF differences between PDD and PD-N, making this comparison a first in the literature. The large effect sizes in post-hoc comparisons strengthen the importance of these results. These observations accord with the previous findings of Babiloni et al. (2017a) and Babiloni et al. (2017b), who reported that the mean IAF was greater in patients who were not cognitively impaired (i.e., HC), compared to a cognitively-impaired PD patients (i.e., those who met criteria for PD-MCI or PDD). In our study we found that after adjusting for UPDRS III, LEDD, and age as covariates, the PD-N versus PD-MCI pairwise difference was no longer significant, but all other comparisons remained significant. Although there is minimal literature on IAF group differences in PD, previous literature has investigated IAF in a longitudinal study investigating whether cognitive decline is associated with slowing of resting state brain activity in PD (Dubbelink et al., 2013). They reported that over a 4-year period, PD patients who were cognitively unimpaired showed a decrease in IAF compared to the HC group.

We did, however, find a linear association between IAF and cognitive Z-score for all participants, indicating that cognitive Z-score and IAF linearly decreased across the HC, PD-N, PD-MCI, and PDD groups. This association between cognitive Z-score and IAF has not previously been investigated. However, a previous study has reported that IAF is a stable neurophysiological trait marker in healthy younger and older adults

(Grandy et al., 2013). They reported that IAF may be a valuable marker for monitoring changes within healthy individuals and a promising marker for monitoring disease progression in individuals over time. This is relevant to our study as we aimed to determine markers for cognitive decline in PD, using HCs as a comparison. In addition, Haegens, Cousijn, Wallis, Harrison, and Nobre (2014), suggested that IAF plays an important and active role in cognitive processing as IAF reflects the focus of attention, which is affected in participants with PD. Our study suggests that as individuals progress to dementia, their mean IAF decreases; if these effects reflect longitudinal changes, then this may help to predict an individual's future level of cognitive impairment.

The association between increased theta spectral power and cognitive impairment was present across all three regions. This frequency band found that spectral power in the PD-MCI and PD-N groups increased across the anterior to central and then to the posterior region. Caviness et al. (2007) outlined spectral power differences in the frontal region that were significantly different between PD-MCI and non-impaired PD groups for the theta band. Fonseca et al. (2013) found theta spectral power was the highest in the PDD group and the lowest in the control group. Our findings are consistent with literature that has reported PD-MCI patients exhibiting significantly higher theta power than the unimpaired PD group (Caviness et al., 2016). Although our findings are similar to previous literature, our study used a novel criterion to classify cognition in PD which identifies PD-MCI participants at increased risk of progression to PDD in the next four years (Myall et al., 2020). Bosboom et al. (2006) also reported that in non-demented PD patients, theta power is increased relative to controls. They also reported that in PDD patients, theta power was also increased, although to a lesser extent compared to the non-demented PD group. Their study used an MMSE score of >28 to characterise their non-demented PD participants, and the DSM-IV criteria for dementia. They did not assess cognitive status in the non-dementia group, whereas our study used Myall et al. (2020) criteria to identify all levels of cognitive impairment in PD. Even though these studies have used varying criteria to classify their patients, there is a significant increase in spectral power in the theta band for PDD patients who have met the criteria for dementia.

Earlier studies have reported group differences within a region but there is minimal literature looking at the group differences across regions. The regions of interest in previous studies vary substantially as most studies define their regions as left and right frontal, central, occipital, and parietal regions, whereas others do not define regions at all (Bousleiman et al., 2014; Caviness et al., 2007; Caviness et al., 2016; Han et al., 2013). Our study used similar regions of interest as we separated 64 electrodes into three regions: frontal, central and parietal. This ensured that we could make direct comparisons between different studies due to the similarity in regions. Other findings from our study show that the PDD group showed increased power from the anterior to central region and then decreased in power from the central to posterior region. Therefore, our study emphasises the group differences between our participant groups, which is prevalent across all regions of interest in this study.

Our findings are consistent with other studies as Caviness et al. (2016) reported that their PDD group had significantly lower alpha power than the PD-MCI group and the PD-MCI group also had lower alpha power than the unimpaired PD group. The association between cognition and spectral power in the alpha band shows the opposite trend to the theta band. In the alpha band the PDD group had the lowest spectral power and this progressively increased across to the PD-MCI, PD-N, and HC groups. This is consistent with previous literature that has reported that in patients with PDD, there was a decrease in relative alpha compared to the non-demented PD group (Bosboom et al., 2006). Ponsen et al. (2012) also reported similar findings where PDD patients had less alpha power in the parieto-temporo-occipital and frontal areas. Our study also found a significant difference between all four groups in the central and posterior region, but no significant group difference in the anterior region. The PDD group's spectral power in the alpha band remained relatively stable across regions. The HC, PD-N, and PD-MCI groups displayed a significant difference in the central and posterior region. This is emphasised by the large effect sizes in these two regions, especially for all pairwise comparisons in the posterior region.

An increase in spectral power in the frequency range below 8 Hz and a decrease in spectral power in ranges above 8 Hz is associated with a risk of cognitive decline in PD, which follows the pattern of results for our study (Babiloni et al., 2011; Caviness

et al., 2016; Klassen et al., 2011; Olde Dubbelink et al., 2013; Stoffers et al., 2008). Our study found that spectral power changes in the alpha band are prominently in the posterior region, which is consistent throughout with the literature indicating that decreased posterior alpha power is associated with a decline in cognition in patients with PD.

Due to the large effect sizes and significant pairwise comparisons in the posterior region of the alpha band, a decision was made to further investigate these differences by looking at the theta/alpha ratio. For the HC and PD-N group, spectral power for this ratio decreased from the anterior to central region and remained relatively stable for the PD-MCI and PDD groups. There was a significant group difference in each region. This has been investigated in a review that focused on biomarkers for cognitive decline in PD (Cozac et al., 2016). They reported that in the studies they reviewed, the theta/alpha ratio, which was taken from directly from the individual studies, was significantly increased in the PDD group compared to the PD-MCI group. They also reported that these ratios had the largest effect sizes to distinguish between the PD-MCI and PDD group. The consistently large effect sizes in our study for the HC, PD-N, PD-MCI, and PDD group in the posterior region may be used in the future to optimally identify patients with PD whose every day cognition will decline in the future. However, due to the minimal literature on spectral power ratios, these results provide a novel insight into the group and regional differences between the theta and alpha power ratio.

Our results contribute to an understanding of IAF differences between cognitive groups and how these differences may be used to assess cognitive decline in PD in the future. There are strengths of the study which increase the value of the findings. The first strength is we extended on limited prior IAF literature in PD, as prior literature has not made a direct comparison between HC, PD-N, PD-MCI, and PDD groups. Another strength is the criteria used to classify cognition. We used a range of PD participants with varying cognition; PD-N, PD-MCI, and PDD, and compared them to HC participants to determine any differences between groups. As Myall et al. (2020) have reported, people with PD who meet the criteria for PD-MCI are at an increased risk of progressing to dementia. This gives the study an advantage to produce initial research that investigates this relationship between a range of cognitive groups in PD and assess progression to PDD in the future using IAF and spectral power measures. By

conducting these EEG sessions, we aimed to determine whether any EEG measures could provide useful biomarkers of brain function.

There was a small sample size of PDD participants compared to the other three cognitive groups due to the lack of PDDs able to participate in the study. This was mainly due to the severity of cognitive decline and the inability for these participants to physically attend the EEG session due to many being in care facilities and unable to attend sessions without a caregiver or significant other. As the EEG equipment is unable to be transported, this limits the experiment to being conducted onsite and as a result those participants who are in care or have severe motor or cognitive disabilities tend to decline participation due to the effort required to come in and participate in the session. Further investigation into PDD participants and increasing the sample size would be ideal, as it would strengthen our findings and statistical power, although due to the severity of cognitive decline, further assessments are often not possible.

When the resting-state task was being conducted, the participant was initially uninterrupted for a ten-minute period to collect the eyes-closed resting state data. Thirty-two participants completed the ten-minute uninterrupted resting state, although these participants were HCs and PD-N participants which are less likely to fall asleep due to their age and cognitive status. Most of these participants were able to be included in the final analysis as they had 180 s of usable data. This was a flaw in the design of the study as we found that participants became significantly drowsy during the 10-min period and on occasion, falling asleep. In order to overcome this problem, the design of the experiment was manipulated to include three epochs of 3-min eyes-closed resting wakefulness. This was done to give the participant a break every three minutes in order to ensure the participant remained awake. Upon analysis, it was made clear that separating the resting state sections was effective as participants provided data that was able to be clearly analysed and included in the final analysis.

In the future, we aim to conduct a follow up EEG session to monitor the progress of the participants and examine associations with decline or stability in cognition over time. Recruiting more PDD participants is also a plan for future research so we can increase the overall sample size to ultimately have a better understanding of how this

disease affects the brain, and the rate at which this deterioration happens over time. This would also be helpful to determine markers for cognitive decline and progression to dementia. Further research also aims to look at a combination of IAF and spectral power measures that could be used collectively to provide an impaired estimate of progression to PDD. Initial key patterns of resting state EEG measures suggest that IAF may be used as a marker for assessing cognition in PD and has the potential to identify cognitive decline. This study may also facilitate clinical interventions as a more targeted approach to the participant's individual treatment for their symptoms can be administered.

6.6 Conclusion

Our study found a significant difference in resting state IAF measures between the four cognitive groups. The HC group displayed the highest IAF, and this decreased in the PD-N, PD-MCI, and PDD group. Spectral power analysis found that the PDD group had higher spectral power in the theta band and lower posterior spectral power in the alpha band, in comparison to the other three groups. These results provide a novel contribution to the literature into determining whether IAF and spectral power can be measures to characterise cognition in PD in the future. Further research into a larger sample of PDD participants and follow up EEG sessions would help strengthen these findings.

Chapter 7: Resting-state functional connectivity

7.1 Introduction

In Chapter 6, spectral power and IAF identified resting-state EEG differences between HC, PD-N, PD-MCI, and PDD groups. IAF in PD-N participants was similar to that in healthy controls (HCs), but was substantially lower on average once patients met the criteria for PD-MCI, and lower again once they met criteria for PDD. In the alpha band, spectral power was the highest in the HC group, but lower once patients met the criteria for PD-MCI, and especially lower when they met criteria for PDD. The differences in alpha power were evident in the posterior brain region, but only PDD showed a marginal difference relative to HC in the anterior region. Spectral power in the theta band was highest for the PDD group compared to the HC group, and intermediate on average for patients with PD-MCI, but not increased in the PD-N group.

The current chapter describes EEG functional connectivity. Functional connectivity assesses synchrony between signals from multiple pairs of electrodes and hence functional activity across brain regions. Functional connectivity is defined as the statistical dependence between EEG signals, which quantifies the interdependence between the time series of EEG across sets of electrodes (Brookes, Woolrich, & Price, 2014; Friston, 2011). This method of analysis focuses on the interdependence of electrode signals by analysing signal phase synchrony, which spectral power does not address (Boon et al., 2017; Stephan et al., 2009). This approach provides new possibilities for quantitative EEG biomarkers to discriminate cognitively impaired patients from those with normal cognition. Functional connectivity is a precursor of network analyses. This provides an additional objective biomarker of cognition in PD that may facilitate prediction of future cognitive decline (Aarsland et al., 2017; Geraedts et al., 2018b).

Functional connectivity has previously been investigated in the literature, but it remains relatively new in the context of PD (Chapter 3; (Arroyave et al., 2019; Ponsen et al., 2012). Functional connectivity, as opposed to spectral power, has the potential for biomarkers that describe local (regional) and distant (cross-regional) functional interactions (Babiloni et al., 2018b; Geraedts et al., 2018b). Local functional connectivity

is measured for every pair of electrodes within a specified region; relatively distant functional interactions between brain regions is based on connectivity between every pair of electrodes across two specified regions (Stephan et al., 2009; Stoffers et al., 2008). Prior research has found a general trend of lower functional connectivity in the alpha band, specifically in the parietal region, in patients with PD who were cognitively impaired (Arroyave et al., 2019; Babiloni et al., 2018b; Bosboom et al., 2009b; Chaturvedi et al., 2019; Olde Dubbelink et al., 2013; Ponsen et al., 2012; Utianski et al., 2016). A decline of functional connectivity in the delta band has also been reported in cognitively impaired PD patients, which was evident in both anterior and parietal regions in PDD compared to non-demented PD patients (Ponsen et al., 2012). For the theta band, however, studies have reported increased functional connectivity in a PD-MCI group compared to a PD-N group (Arroyave et al., 2019; Chaturvedi et al., 2019; Olde Dubbelink et al., 2013).

The previous PD literature on functional connectivity has used different methodology to assess cognition and often lacked detailed cognitive testing. These studies have used criteria based on MDS Task Force criteria, Mini-mental State Examination (MMSE) scores, and the DSM-IV for dementia, to classify cognition in PD patients (Arroyave et al., 2019; Babiloni et al., 2018b; Bertrand et al., 2016; Boon et al., 2017; Bosboom et al., 2009b; Chaturvedi et al., 2019; Geraedts et al., 2018b; Hassan et al., 2017; Moazami-Goudarzi et al., 2008; Olde Dubbelink et al., 2013; Ponsen et al., 2012; Teramoto et al., 2016; Utianski et al., 2016). MMSE scores are not ideal for assessing MCI and may misclassify patients as showing dementia or not, yet alone cognitive impairment (Burdick et al., 2014; Nieuwenhuis-Mark, 2010). Specific MDS criteria for PDD were introduced because previous definitions had problems (B. Dubois et al., 2007a). For PD-MCI, only a few studies (Babiloni et al., 2018b; Chaturvedi et al., 2019; Hassan et al., 2017; Utianski et al., 2016) have included patients classified using MDS criteria; most studies classified their patients as ‘non-demented’, so samples would include a varying proportion of PD-N and PD-MCI patients (Bosboom et al., 2009a; Geraedts et al., 2018b; Ponsen et al., 2012). These studies reported overall that PD-MCI had lower functional connectivity in the alpha band compared to the HC and PD-N group, and higher functional connectivity was observed in the theta band for PD-MCI participants compared to the PD-N, and HC groups.

Only one study to our knowledge has directly compared functional connectivity differences across four groups, namely HC, PD-N, PD-MCI and PDD, although only pairwise comparisons (HC vs PD-N; PD-N vs PD-MCI; PD-N vs PDD) were made (Utianski et al., 2016). Among a more complex set of measures of functional connectivity, they included phase lag index (PLI) but not a weighted PLI measure. They reported that functional connectivity, averaged across the whole brain, was lower in the PDD group (N=18) compared to PD-N group (N=57) for the alpha band; the PD-N group was similar to the HC group (N=57) on this measure. An intermediate effect was found in the PD-MCI group, but this was not significant, and they caution that this group included only 13 patients. For the theta band, they also reported that the PD-N group showed higher PLI functional connectivity than the HC group, with some evidence that this increased further in the PD-MCI group, but surprisingly not in the PDD group. Increased theta band functional connectivity in the PD-N group is perhaps surprising, because other studies have reported lower functional connectivity for their non-dementing PD group, compared to their HC group (Moazami-Goudarzi et al., 2008). The study by Utianski et al. (2016) classified patients as PD-N or PD-MCI using assessments that approximated the MDS criteria. However, they included only thirteen PD-MCI patients and comment that their findings for this group are therefore only preliminary. Due to the limited prior functional connectivity literature in PD-MCI, the current study made a direct comparison between a HC, PD-N, PD-MCI and PDD group. Non-dementing patients were classified using the current NZBRI PD-MCI criteria (Myall et al., 2020) and a larger sample of PD-MCI patients was used.

Another issue, highlighted in Chapter 3, is that previous literature has used various measures to assess functional connectivity. The most common measures are coherence (Arroyave et al., 2019; Babiloni et al., 2018b; Bertrand et al., 2016; Bosboom et al., 2009a; Moazami-Goudarzi et al., 2008; Teramoto et al., 2016), and phase lag index (PLI) (Chaturvedi et al., 2019; Geraedts et al., 2018; Hassan et al., 2017; Olde Dubbelink et al., 2013; Ponsen et al., 2012; Utianski et al., 2016). These two measures did not appear to influence the pattern of results, at least for the alpha band across the literature. However, Utianski et al. (2016) has increased theta in the PD-N group and they also found no extra increase in PDD which may be a result of the functional connectivity measure used between studies. However, the major problem with the

coherence measure concerns volume conduction (Bowyer, 2016). Volume conduction can result in artificially high coherence values, especially for electrodes that are close to each other (Bastos & Schoffelen, 2015). PLI is the other common functional connectivity measure used to estimate connectivity in EEG and is more accurate than coherence (Hardmeier et al., 2014). However, PLI is also susceptible to volume conduction and noise and can underestimate the connectivity at small time lags and low signal-to-noise ratio (Bastos & Schoffelen, 2015; Vinck et al., 2011). To overcome this issue, the debiased weighted phase lag index (dwPLI) measure has been developed to help minimise the type of bias inherent to PLI (Vinck et al., 2011).

Based on the complications outlined above regarding functional connectivity measures, and in order to mitigate these issues, the current study uses a debiased measure of phase synchrony (i.e., dwPLI) to estimate functional connectivity. This potential solution has been described in Chapter 3, section 3.3.2 (Vinck et al., 2011). The debiased wPLI is both less sensitive to volume conduction and reduces the estimation bias. Currently, the dwPLI has only started to be used as a functional connectivity measure in the PD literature and the effects across the spectrum of cognitive groups have not yet been assessed (Iyer, Au, Angwin, Copland, & Dissanayaka, 2020). This chapter uses the same participants as Chapter 6, who had their cognitive status classified on the basis of the ten sensitive neuropsychological tests outlined by Myall et al. (2020). These tests identify PD-MCI patients who are at high relative risk (RR) of conversion to PDD in the next four years (RR = 8), rather than simply patients who have some cognitive impairment on any test and who may not be showing high risk of conversion (Barker & Williams-Gray, 2014).

7.2 Method

7.2.1 Participants

Participants used in this study are the same as Chapter 6, section 7.2.1.

7.2.2 EEG Recordings

The EEG recordings followed the same procedure as Chapter 6, section 7.2.2.

7.2.3 EEG Analysis

The initial EEG analysis and exclusions are the same as Chapter 6 (section 6.2.4). We calculated functional connectivity in the following frequency ranges (Hz): 0.5-4 (delta), 4-8 (theta), 8-12 (alpha), and 13-29 (beta). Functional connectivity was calculated using the debiased wPLI, which uses a phase-difference weighting normalisation to minimise volume conduction and achieve more accurate and valid measures.

Functional connectivity was first computed for all pairs of electrodes within each of the three regions. The three regions were defined as Anterior, Central, and Posterior, as outlined in Chapter 6, section 6.2.3. The within-region connectivity was estimated by averaging the functional connectivity between all electrode pairs that were in the same region, to derive a single measure per region per person. Secondly, a between-region connectivity was estimated by averaging connectivity values between all electrode pairs belonging to two different regions. That is, the between-region analyses were defined as Anterior and Posterior, Anterior and Central, and Posterior and Central.

7.2.4 Statistical Analysis

R version 3.6.3 was used to conduct statistical analyses. Functional connectivity was analysed using a two-way ANCOVA with age and sex as covariates. As neither age nor sex were statistically significant for the within-region functional connectivity analysis (all $F < 1.75$, $df = 1, 119$, $p > 0.19$), and the between-region functional connectivity analysis, (all $F < 1.60$, $df = 1, 119$, $p > 0.21$), and did not change the outcomes for other variables, the unadjusted model was used to show mean values for functional connectivity. Functional connectivity in each of the four frequency bands was analysed separately. For all analyses, Group was the between-subject factor and Region was the repeated-measures factor.

7.3 Results

7.3.1 Participant Demographics and Group Characteristics

Participant demographics and group characteristics are as per Chapter 6, section 6.3.

7.3.2 Within-Region Functional Connectivity, for Anterior, Central, and Posterior Regions

There were no significant Group × Region interactions for any of the four frequency bands (all $F < 1.80$, all $p > 0.10$; Figure 7.1). The HC and PD-N groups showed very similar mean values for functional connectivity for all frequency bands. There were significant main effects of Group for both theta ($F(3, 119) = 4.84$, $p < 0.01$) and alpha bands ($F(3, 119) = 3.25$, $p < 0.05$). Post-hoc tests confirmed that functional connectivity in the theta band was significantly higher for the PDD group compared the HC and PD-N groups. By contrast, functional connectivity in the alpha band was lower in the PDD group compared to the HC and PD-N groups. For both bands, the PD-MCI group had intermediate functional connectivity values that did not differ significantly from other groups. However, there was no evidence of a difference across groups for functional connectivity in delta ($F(3, 119) = 1.37$, $p = 0.25$), and beta bands ($F(3, 119) = 0.04$, $p = 0.99$). Pairwise comparisons are shown for interest in Table 7.1 – 7.4.

Collapsed across groups (i.e. ignoring group status), there was a pattern of higher functional connectivity in both central and posterior regions, compared to the anterior region, in the theta, alpha, and beta bands (all $F(2, 240) > 10.12$, $p < 0.001$). In the delta band, the functional connectivity, collapsed across groups, in the posterior region was higher than the functional connectivity in the anterior region ($F(2, 240) = 14.95$, $p < 0.001$).

As alpha functional connectivity had a clear main effect, both here and for the previous measure of alpha power (Chapter 6), this measure was chosen to investigate the association with global Z-score (average across the 10 tests), but excluding the PDD group as few PDD patients took these 10 tests (see Chapter 6). As there was no evidence of an interaction between group and region, the connectivity measures were averaged over the three regions. Alpha functional connectivity declined as cognition declined, but the association was relatively weak (alpha functional connectivity and global Z-score, $r = 0.26$, $p = 0.01$; Figure 7.2).

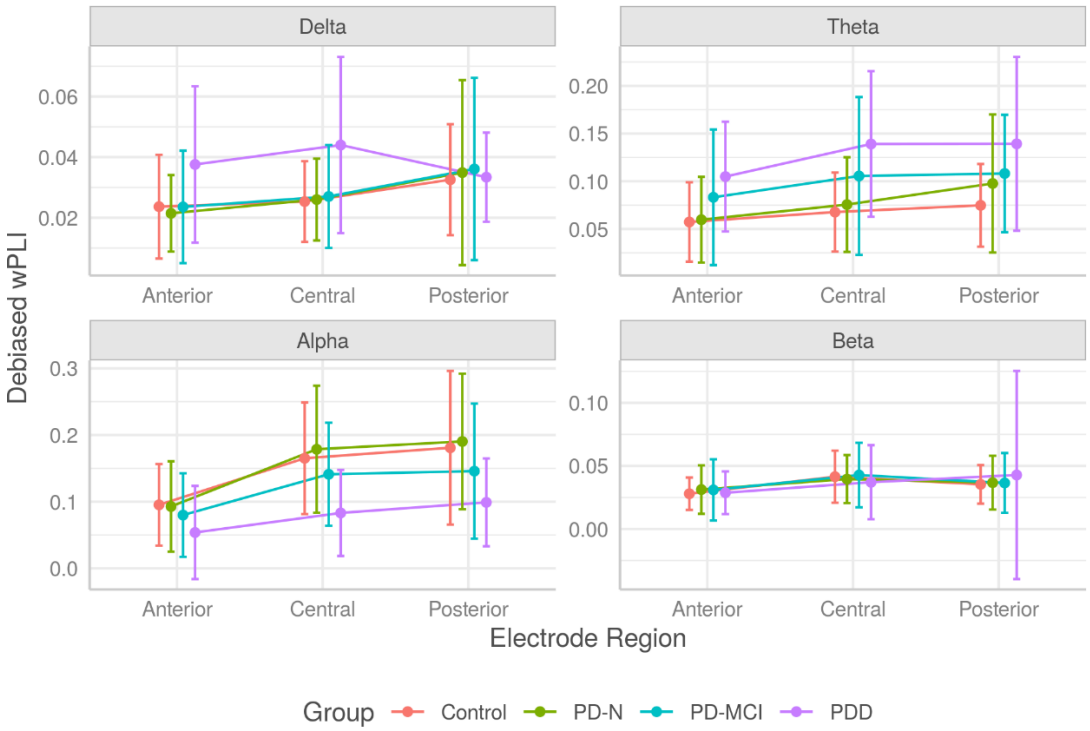

Figure 7.1 Functional connectivity for the four frequency bands for the HC, PD-N, PD-MCI, and PDD groups, across the three electrode regions.

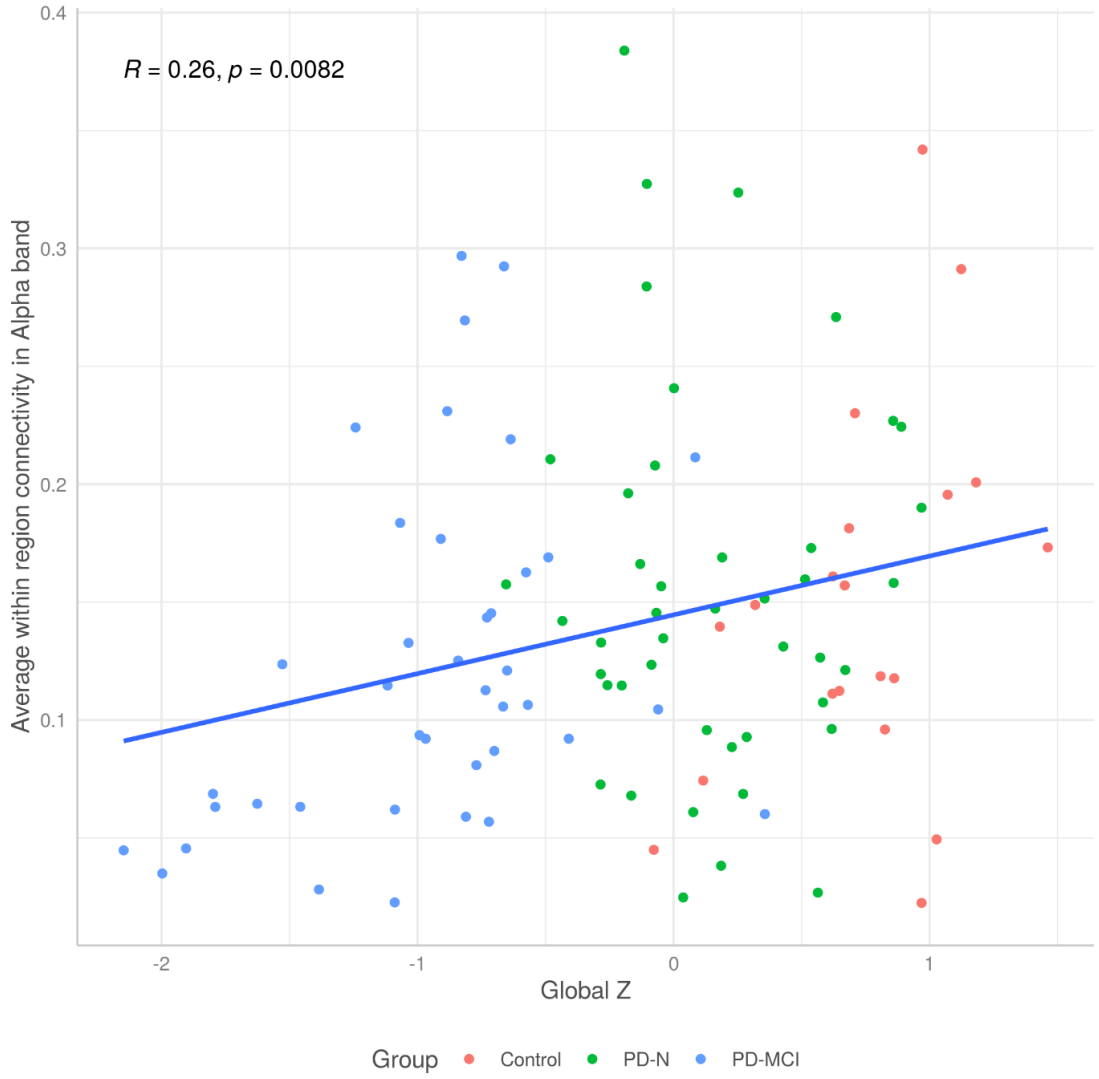

Figure 7.2 Scattergram of functional connectivity for the Alpha band with aggregate Z-score for the ten neuropsychological measures, for the HC, PD-N, and PD-MCI groups, averaged across all regions.

Table 7.1 Delta band within-region functional connectivity differences in the four groups, collapsed across regions.

Cognitive Group	Difference	t ratio	p value	Effect size (±95%CI)
HC - PD-N	-0.00	-0.22	0.996	-0.06 (-0.63, 0.51)
HC - PD-MCI	-0.00	-0.48	0.963	-0.13 (-0.68, 0.41)
HC - PDD	-0.01	-1.94	0.219	-0.74 (-1.50, 0.03)
PD-N - PD-MCI	-0.00	-0.28	0.992	-0.07 (-0.56, 0.42)
PD-N - PDD	-0.01	-1.80	0.277	-0.67 (-1.42, 0.08)
PD-MCI - PDD	-0.01	-1.65	0.355	-0.60 (-1.34, 0.36)

Abbreviations: PDN = Participants with PD who have relatively normal cognition (i.e. do not meet the criteria for PDMCI); PDMCI = PD with mild cognitive impairment; PDD = PD with dementia; C.I = Confidence interval

Table 7.2 Theta band within-region functional connectivity differences in the four groups, collapsed across regions.

Cognitive Group	Difference	t ratio	p value	Effect size (±95%CI)
HC - PD-N	-0.01	-0.83	0.839	-0.03 (-1.00, 0.41)
HC - PD-MCI	-0.03	-2.46	0.072	-0.84 (-1.54, -0.14)
HC - PDD	-0.06	-3.35	0.006	-1.58 (-2.56, -0.59)
PD-N - PD-MCI	-0.02	-1.77	0.294	-0.54 (-1.16, -0.08)
PD-N - PDD	-0.05	-2.77	0.033	-1.23 (-2.23, -0.33)
PD-MCI - PDD	-0.03	-1.63	0.367	-0.74 (-1.64, 0.17)

Abbreviations: PDN = Participants with PD who have relatively normal cognition (i.e. do not meet the criteria for PDMCI); PDMCI = PD with mild cognitive impairment; PDD = PD with dementia; C.I = Confidence interval

Table 7.3 Alpha band within-region functional connectivity differences in the four groups, collapsed across regions.

Cognitive Group	Difference	t ratio	p value	Effect size (±95%CI)
HC - PD-N	0.00	0.15	0.999	0.06 (-0.71, 0.83)
HC - PD-MCI	0.03	1.56	0.404	0.58 (-0.17, 1.33)
HC - PDD	0.07	2.68	0.041	1.38 (0.33, 2.44)
PD-N - PD-MCI	0.03	1.57	0.400	0.53 (-0.15, 1.20)
PD-N - PDD	0.07	2.63	0.048	1.33 (0.29, 2.36)
PD-MCI - PDD	0.04	1.62	0.374	0.80 (-0.19, 1.79)

Abbreviations: PDN = Participants with PD who have relatively normal cognition (i.e. do not meet the criteria for PDMCI); PDMCI = PD with mild cognitive impairment; PDD = PD with dementia; C.I = Confidence interval

Table 7.4 Beta band within-region functional connectivity differences in the four groups, collapsed across regions.

Cognitive Group	Difference	t ratio	p value	Effect size (±95%CI)
HC - PD-N	-0.00	-0.07	1.000	-0.20 (-0.58, 0.54)
HC - PD-MCI	-0.00	-0.31	0.990	-0.08 (-0.62, 0.45)
HC - PDD	-0.00	-0.18	0.998	-0.07 (-0.80, 0.67)
PD-N - PD-MCI	-0.00	-0.26	0.994	-0.06 (-0.54, 0.42)
PD-N - PDD	-0.00	-0.13	0.999	-0.05 (-0.77, 0.68)
PD-MCI - PDD	0.00	0.05	1.000	-0.02 (-0.69, 0.72)

Abbreviations: PDN = Participants with PD who have relatively normal cognition (i.e. do not meet the criteria for PDMCI); PDMCI = PD with mild cognitive impairment; PDD = PD with dementia; C.I = Confidence interval

7.3.3 Between-Region Functional Connectivity

There were significant main effects of Group for both theta ($F(3, 119) = 5.67$, $p < 0.001$) and alpha bands ($F(3, 119) = 3.21$, $p = 0.026$) (Figure 7.3). This is also demonstrated by the spectrum grand averages for dwPLI in Figure 7.4. This figure shows visually the increase in functional connectivity for the PDD group and the decreased functional connectivity for the alpha band. Post-hoc tests confirmed that functional connectivity in the theta band was significantly higher for the PDD group compared to the HC and PD-N groups, and for the PD-MCI group compared to the HC group. By contrast, functional connectivity in the alpha band was significantly higher for the HC and PD-N groups compared to the PDD group. For this band PD-MCI showed no difference between any of the other three groups. However, there was no evidence of a difference across groups for the functional connectivity in the delta ($F(3, 119) = 1.75$, $p = 0.16$) and beta bands ($F(3, 119) = 0.10$, $p > 0.9$). Pairwise comparisons and effect sizes are shown for interest in Table 7.5 – 7.8.

There were main effects of Region-pairs for all four bands (all $F > 5.26$, $p < 0.01$). Post-hoc analysis showed that, collapsed across groups, there was a pattern of higher functional connectivity between the posterior and central region, compared to between the anterior and posterior region, in the alpha and beta bands (all $t > 2.99$, $p < 0.01$). In the alpha band, the functional connectivity between the posterior and central region was higher than the functional connectivity between the anterior and central region ($t(240) = 6.8$, $p < 0.001$). In the beta band, the functional connectivity, between the anterior and central region was higher than the functional connectivity between the anterior and posterior region ($t(240) = 5.6$, $p < 0.001$).

The only band to produce a significant Group × Region interaction was the delta band ($F(3, 240) = 3.03$, $p = 0.007$). Post-hoc analysis found that functional connectivity between the anterior and central region was significantly higher in the PDD group compared to that in the HC, PD-N, and PD-MCI groups ($F(3, 161) = 3.85$, $p = 0.01$). There was also an effect of region for the PD-N, PD-MCI and PDD group ($p < 0.05$), but there was no regional difference for the HC group ($p = 0.37$).

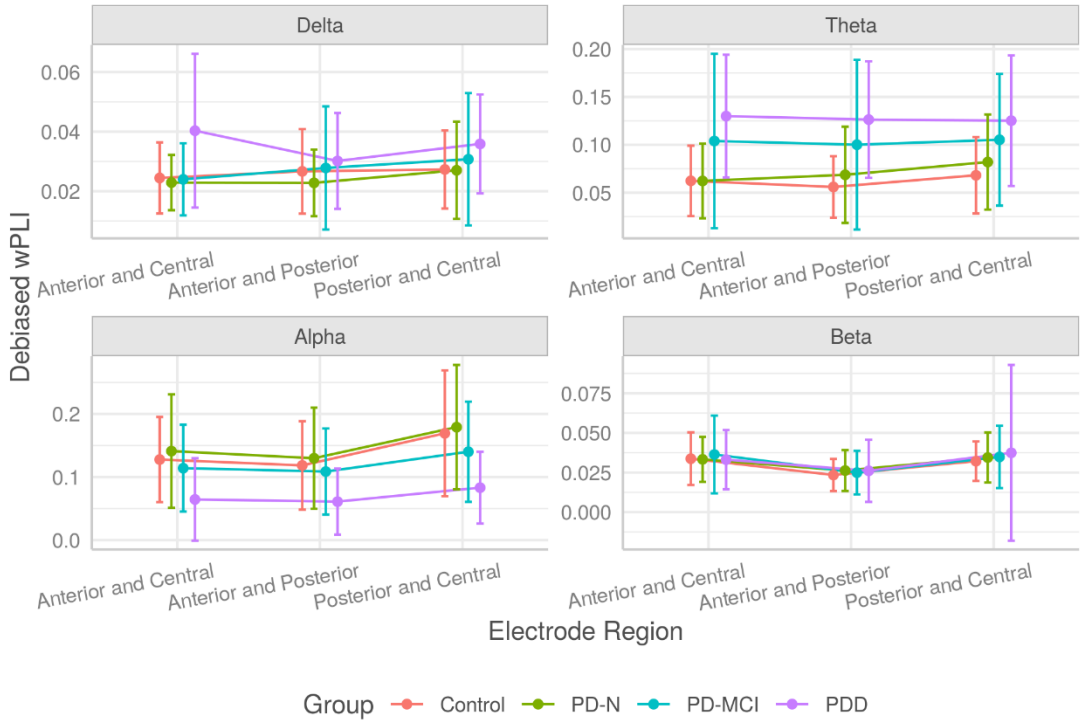

Figure 7.3 Functional connectivity for four frequencies in the four groups and between the three electrode regions.

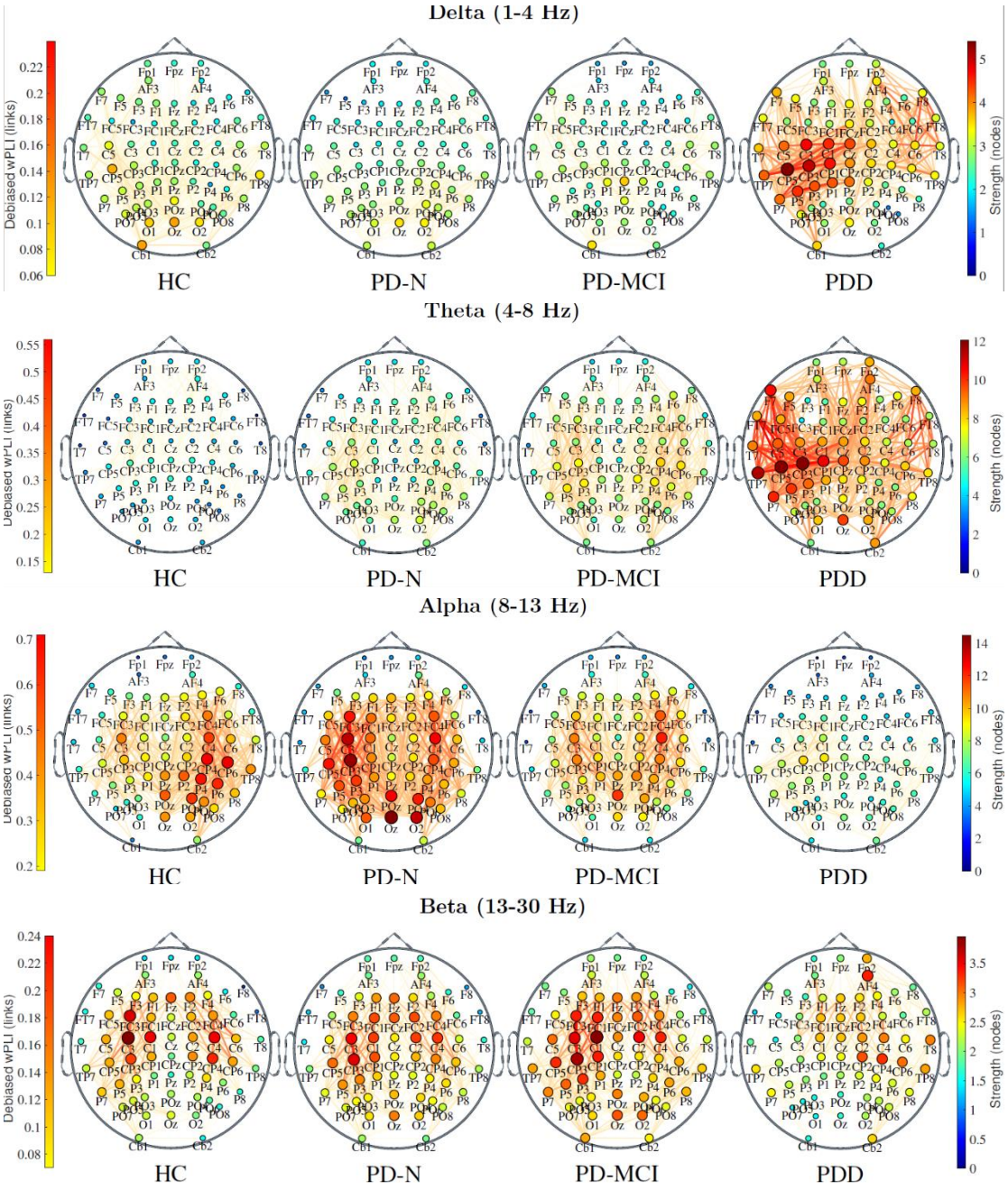

Figure 7.4 dwPLI spectrum grand averages for the delta, theta, alpha and beta wave.

Table 7.5 Delta band inter-regional functional-connectivity differences in the four groups, collapsed across regions.

Cognitive Group	Difference	t ratio	p value	Effect size (±95%CI)
HC - PD-N	0.00	0.41	0.977	0.20 (-0.75, 1.14)
HC - PD-MCI	-0.00	-0.42	0.974	-0.19 (-1.10, 0.71)
HC - PDD	-0.01	-1.88	0.244	-1.18 (-2.45, 0.09)
PD-N - PD-MCI	-0.00	-0.95	0.780	-0.39 (-1.21, 0.43)
PD-N - PDD	-0.01	-2.23	0.122	-1.38 (-2.63, -0.12)
PD-MCI - PDD	-0.01	-1.63	0.364	-0.99 (-2.20, 0.23)

Abbreviations: PDN = Participants with PD who have relatively normal cognition (i.e. do not meet the criteria for PDMCI); PDMCI = PD with mild cognitive impairment; PDD = PD with dementia; C.I = Confidence interval

Table 7.6 Theta band inter-regional functional-connectivity differences in the four groups, collapsed across regions.

Cognitive Group	Difference	t ratio	p value	Effect size (±95%CI)
HC - PD-N	-0.01	-0.62	0.925	-0.39 (-1.62, 0.85)
HC - PD-MCI	-0.04	-2.84	0.027	-1.70 (-2.92, -0.47)
HC - PDD	-0.07	-3.26	0.008	-2.67 (-4.39, -0.96)
PD-N - PD-MCI	-0.03	-2.44	0.075	-1.31 (-2.40, -0.22)
PD-N - PDD	-0.06	-2.84	0.027	-2.29 (-3.95, -0.63)
PD-MCI - PDD	-0.02	-1.24	0.601	-0.98 (-2.55, 0.59)

Abbreviations: PDN = Participants with PD who have relatively normal cognition (i.e. do not meet the criteria for PDMCI); PDMCI = PD with mild cognitive impairment; PDD = PD with dementia; C.I = Confidence interval

Table 7.7 Alpha band inter-regional functional-connectivity differences in the four groups, collapsed across regions.

Cognitive Group	Difference	t ratio	p value	Effect size (±95%CI)
HC - PD-N	-0.00	-0.11	0.999	-0.07 (-1.30, 1.16)
HC - PD-MCI	0.02	1.15	0.657	0.69 (-0.50, 1.87)
HC - PDD	0.07	2.68	0.042	2.19 (0.51, 3.87)
PD-N - PD-MCI	0.02	1.41	0.493	0.76 (-0.31, 1.82)
PD-N - PDD	0.07	2.82	0.029	2.26 (0.61, 3.91)
PD-MCI - PDD	0.05	1.92	0.227	1.50 (-0.08, 3.09)

Abbreviations: PDN = Participants with PD who have relatively normal cognition (i.e. do not meet the criteria for PDMCI); PDMCI = PD with mild cognitive impairment; PDD = PD with dementia; C.I = Confidence interval

Table 7.8 Beta band inter-regional functional-connectivity differences in the four groups, collapsed across regions.

Cognitive Group	Difference	t ratio	p value	Effect size (±95%CI)
HC - PD-N	-0.00	-0.17	0.998	-0.07 (-0.75, 0.71)
HC - PD-MCI	-0.00	-0.46	0.968	-0.17 (-0.92, 0.57)
HC - PDD	-0.00	-0.42	0.976	-0.22 (-1.25, 0.82)
PD-N - PD-MCI	-0.00	-0.31	0.990	-0.11 (-0.78, 0.57)
PD-N - PDD	-0.00	-0.29	0.991	-0.15 (-1.16, 0.87)
PD-MCI - PDD	-0.00	-0.09	1.000	-0.04 (-1.03, 0.95)

Abbreviations: PDN = Participants with PD who have relatively normal cognition (i.e. do not meet the criteria for PDMCI); PDMCI = PD with mild cognitive impairment; PDD = PD with dementia; C.I = Confidence interval

7.4 Discussion

The main finding from this study was that functional connectivity differences between groups were present for the alpha band and the theta band. For the within-region analysis, functional connectivity in the alpha band was lower for the PDD group relative to the HC and PD-N groups, which did not differ. The PD-MCI group showed intermediate alpha functional connectivity that was not reliably different to other groups, but this may reflect the small sample size for the PDD group (N = 12). The group differences in alpha functional connectivity did not change appreciably across region, although again this may be a sample size issue. In the theta band, functional connectivity was higher for the PDD group, irrespective of region. The HC and PD-N group showed the lowest theta functional connectivity and there was no difference between these two groups. The PD-MCI group had intermediate theta functional connectivity values that did not differ significantly from other groups. For the between-region connectivity, the pattern of findings was similar to the within-region analysis except the PD-MCI group showed an intermediate effect in the theta between-region connectivity and showed a significant difference compared to the HC and PD-N group between the anterior and central region. However, for alpha band between-region connectivity, the PD-MCI group were similar to the PD-N and HC groups than was the case for the within-region alpha band connectivity.

The within-region findings for our study are consistent with other cross-sectional functional connectivity studies in PD. Most studies compared regional differences using anterior, central, and posterior regions (Bertrand et al., 2016; Moazami-Goudarzi et al., 2008; Teramoto et al., 2016), but several studies included left and right differences and separated their posterior region into parietal and occipital (Arroyave et al., 2019; Babiloni et al., 2018b; Bosboom et al., 2009b; Chaturvedi et al., 2019; Geraedts et al., 2018b; Olde Dubbelink et al., 2013). These differences in regional comparisons did not affect the overall findings between these studies in the literature. One study did not separate regions and assessed only the whole brain (Utianski et al., 2016); that study, however, reported that theta functional connectivity is higher in PD-N compared to HC, and only mildly increased further in PDD, which is at odds with both the current study, Moazami-Goudarzi et al. (2008), and Bertrand et al. (2016).

The majority of prior research has used non-demented PD participants and made comparisons to a PDD group (Arroyave et al., 2019; Bertrand et al., 2016; Bosboom et al., 2009b; Hassan et al., 2017; Ponsen et al., 2012; Utianski et al., 2016). These studies found a general trend of lower functional connectivity the alpha band among PDD patients, compared to non-demented PD participants and HCs. When making comparisons with a PD-MCI group, there was one study who reported that the PD-MCI group had higher functional connectivity in the alpha band compared to the PD-N group, which differs from most of the other literature (Arroyave et al., 2019). Other studies have reported higher functional connectivity for the PD-MCI group in the theta band compared with the PD-N group (Arroyave et al., 2019; Chaturvedi et al., 2019). In our study, the PDD group had significantly lower functional connectivity, as expected, than the non-demented PD groups in the alpha band using the debiased weighted phase lag index (dwPLI) for functional connectivity. Using this method of analysing functional connectivity did not produce findings that were significantly different from the literature, even though most previous functional connectivity PD literature used PLI or coherence as their analysis measure (Lau et al., 2012; Mehraram et al., 2020; Vinck et al., 2011).

Regional differences have been assessed in the literature using mainly the anterior, central, parietal, or posterior which includes the parietal and occipital electrodes (Babiloni et al., 2018b; Bosboom et al., 2009b; Ponsen et al., 2012). The cross-regional connectivity measures also accord with previous studies, despite these studies using different regions of interest. Babiloni et al. (2018a) and Bosboom et al. (2009a) used the anterior and central which was the same as our study, but included the parietal, occipital, and temporal regions, whereas Ponsen et al. (2012) looked at 68 regions of interest. Despite the differences in regions, overall, our results found that the PDD patients had higher functional connectivity in the theta band, compared to HCs. In contrast, the PDD group had lower functional connectivity in the alpha band compared to the HC and PD-N group. Thus, patients with PD who are cognitively impaired have lower alpha functional connectivity and increased theta functional connectivity compared with PD-N patients. These posterior differences for the PD participants may be attributed to disease progression and the dual-syndrome hypothesis.

We found no significant differences between groups for the beta band. This differs from previous studies which have reported that PD-MCI groups had lower functional connectivity in the anterior region for the beta band than the PD-N group, which had been classified using the MDS Task Force criteria (Arroyave et al., 2019; Chaturvedi et al., 2019). These differences may be attributed to the measure used to derive functional connectivity as debiased wPLI is especially resistant to volume conduction, and is able to detect more complex variability in the data (Lau et al., 2012; Vinck et al., 2011). Vinck et al. (2011) and Hardmeier et al. (2014) reported that PLI is susceptible to phase perturbations due to its inherently discrete nature. The anterior regions used in both our study and Arroyave et al. (2019) and Chaturvedi et al. (2019) did not differ, however Arroyave et al. (2019) classified their participants using the MDS Level I criteria which may identified participants as PD-MCI who would not have met the PD-MCI criteria if classified using the NZBRI criteria and explain the differences in the literature.

Other studies have reported lower parietal delta band functional connectivity in cognitively impaired groups compared to HCs (Olde Dubbelink et al., 2013; Ponsen et al., 2012). Whereas our study found significant differences in the delta band between the anterior and central region as the PDD group had higher functional connectivity in comparison to the HC, PD-N, and PD-MCI groups. These findings differ from Ponsen et al. (2012) who reported PDD patients had lower delta functional connectivity in the fronto-temporal region compared to the non-demented PD group. The main overall effects from our study suggest that as individuals progress to dementia, functional connectivity decreases in the alpha band and increases in the theta band. If these effects reflect longitudinal changes, then this may help to predict an individual's future level of cognitive impairment.

The results from this chapter contribute to the functional connectivity literature by investigating group differences in PD and how these differences may be used to assess cognitive decline in PD in the future. The functional connectivity results are similar to the spectral power results in Chapter 6, but the spectral power results had larger effect sizes than the functional connectivity. Despite the results not providing as strong findings as the spectral power analysis, there are some strengths of the study which

increase the significance of the findings. The first strength of the study is that we investigated functional connectivity by making a direct comparison between a HC, PD-N, PD-MCI, and PDD group. Utianski et al. (2016) included HC, PD-N, PD-MCI and PDD participants, although they used MMSE and MoCA scores to characterise their patient groups, which may not completely identify cognitive decline as well as other classification criteria such as the MDS Task Force criteria (Litvan et al., 2012). This is because MMSE scores are not ideal for assessing MCI and may misclassify patients as showing dementia or not, yet alone cognitive impairment (Burdick et al., 2014; Nieuwenhuis-Mark, 2010). We have extended on prior literature by investigating functional connectivity in a HC, PD-N, PD-MCI and PDD group using the more specific adaptation of Myall et al. (2020) for PD-MCI, which is accordance with Level II criteria, which has a relative risk (RR) of 8 for progression to PDD in the next four years. The MDS Task Force Level II criteria does not specify neuropsychological tests to use for classifications, and Myall et al. (2020) has identified those tests with higher risk of progression to PDD. The second strength of the study was using the debiased wPLI method for deriving functional connectivity, which Vinck et al. (2011) report has been developed to minimise the bias that is inherent to PLI. To our knowledge this method has only started to be investigated in the PD literature (Iyer et al., 2020) before which adds a novel aspect to our study and is a reliable measure to assess functional connectivity group differences.

The limitations are the same as for Chapter 6. The main limitation is the small number of PDD participants in the study. This was due to the participants not being able to attend their EEG session as a result of the severity of their cognitive status and the inability for these participants to physically attend the EEG session due to many being in care facilities and unable to attend sessions without a caregiver or significant other. Another limitation was the method of data collection. Our study collected eyes-closed resting state wakefulness, whereas other studies have collected eyes-open resting state or a both eyes-open and eyes-closed resting wakefulness (Bosboom et al., 2006; Fonseca et al., 2009; Ponsen et al., 2012). Therefore, future work could investigate the differences between eyes-closed resting wakefulness and eyes-open wakefulness in PD to determine if there are any significant differences between the two conditions. In the future we aim to conduct a follow up EEG resting state study to examine longitudinal

changes of functional connectivity measures and examine associations with decline or stability in cognition over time. Recruiting more PDD participants would be beneficial to the study to increase the sample size and statistical power. Further research also aims to look at whether a combination of IAF, spectral power, and functional connectivity measures that could be used collectively to provide markers for classifying participants cognitive status. Conducting a follow up study would also provide further insight into the effect on functional connectivity measures alongside disease progression.

7.5 Conclusion

The aim of the current analysis was to determine functional connectivity measures to characterise cognitive status in PD. For this purpose, debiased wPLI functional connectivity measures were investigated. The overall trend suggests that there is a relationship between functional connectivity in the alpha and theta band, and cognition. Our study found that in the within-region analysis, functional connectivity in the theta band was significantly higher for the PDD group compared the HC and PD-N groups. By contrast, functional connectivity in the alpha band was lower in the PDD group compared to the HC and PD-N groups. For both bands, the PD-MCI group had intermediate functional connectivity values that did not differ significantly from other groups. Furthermore, in the between-region analysis functional connectivity in the theta band was significantly higher for the PDD group compared to the HC and PD-N groups, and for the PD-MCI group compared to the HC group. By contrast, functional connectivity in the alpha band was significantly higher for the HC and PD-N groups compared to the PDD group. For this band PD-MCI showed no difference between any of the other three groups. These results provide a novel contribution to the literature by using the debiased wPLI measure for functional connectivity to make a direct comparison between a HC, PD-N, PD-MCI, and PDD groups, to determine whether functional connectivity could be a measure used to characterise cognition in PD in the future. Further research into a larger sample size of PDD participants and follow-up EEG for the non-dementia PD groups would strengthen the value of the dwPLI connectivity measure.

Chapter 8: Key findings, critique, and concluding remarks

8.1 Key Findings

This thesis examined the relationship between spontaneous resting-state EEG, three-stimulus visual oddball task ERPs, and cognitive status in Parkinson's disease. The first two studies addressed ERP differences using three-stimulus visual oddball tasks and the second two studies addressed spectral power and functional connectivity measures to identify group differences during resting wakefulness. These studies allowed a direct comparison between four cognitive groups – HC, PD-N, PD-MCI, and PDD to identify potential markers of cognitive decline in PD. The PD-N and PD-MCI groups were classified using current NZBRI criteria, which use a selection of neuropsychological tests to identify cognitively-impaired patients considered to be at high risk of conversion to PDD within the next four years.

Task difficulty, based on an "easy" versus a "harder" three-stimulus visual oddball task, did not influence any P300 ERP measures, or produce any significant differences between an initial sample of HC and PD-N participants. Nonetheless, a difficulty effect was evident because reaction times were increased in the "harder" version. Also, PD-N participants also took longer to respond to the target stimulus compared to the HC participants. The second ERP study focused on the 'easy' task only which included a HC, PD-N, PD-MCI, and PDD group to determine effects on P3a and P3b amplitude and latency between groups. There were, however, no significant group differences of P300 amplitude or P300 latency across HC, PD-N, PD-MCI and PDD groups. There was an overall pattern of gradual reduction of latency for P3a and P3b ERPs from the anterior to the posterior region, irrespective of groups. There was also an overall pattern of increase in P3a and P3b amplitude for the PD-N group in the posterior region, compared to HCs, but this was not significant. Moreover, reaction time across groups was shortest for the HC group but progressively increased in the PD-N, PD-MCI and PDD group.

During resting wakefulness, IAF did not differ significantly between the HC and PD-N groups but was lower in the PD-MCI group and even lower in the PDD

group. When analysing the PD groups, LEDD, sex, and age were used as covariates, but this did not change the findings, so the unadjusted values were used to report IAF. Spectral power differences in our sample were clearest in the alpha and theta band. In the theta band, spectral power was lowest in the HC and PD-N groups and increased, on average, once participants met the criteria for PD-MCI, and especially for PDD. In the alpha band, spectral power was lower in the PDD group than the other three groups. However, the pattern of effects for spectral power in the alpha band varied across region for the HC, PD-N, and PD-MCI groups. Both the HC and PD-N groups showed an increase in alpha power from the anterior region to central region and then again to the posterior region. The PD-MCI group did not show an increase from central to posterior region. Alpha power for posterior region revealed differences across all four groups, with a gradual decrease in alpha power across HC, PD-N, PD-MCI, and PDD groups. The only difference for the delta band was that the PDD group did not show the decrease in power from the anterior to central to posterior region which was evident in the other three groups. The main outcome with respect to beta power was that the PDD group showed no change in power across regions and lower power in the anterior and central regions compared to the other groups, which all showed a reduction in beta power for the posterior region.

In terms of the dwPLI functional connectivity, group differences were again evident for the theta band and alpha band. For functional connectivity measures derived within each of the three regions, no differences were evident between HC and PD-N for either band. Compared to HC and PD-N, the PDD group showed higher functional connectivity for the theta band and lower connectivity for the alpha band. Although the difference between PD-MCI and PDD was not significantly different, the PD-MCI group had intermediate values between PD-N and PDD. This intermediate difference values for the PD-MCI between the PD-N and PDD group were evident irrespective of region. No group differences in functional connectivity were found for delta or beta bands.

Similar findings were evident when functional connectivity was assessed across pairs of regions (anterior vs central; anterior vs posterior; central vs posterior), instead of within region. That is, only overall group main effects were evident, and differences

found only for theta (higher in PDD) and alpha (lower in PDD). However, PD-MCI showed similar functional connectivity to HC and PD-N for alpha, but values that were intermediate for theta.

Effect sizes were calculated for all resting-state measures which emphasised the size of the group differences for the IAF, spectral power, and functional connectivity measures. The pattern of findings for IAF and the associated effect sizes suggest that IAF could be a useful, easily derived EEG measure associated with cognitive status in PD. If the effect sizes here can be generalized, then a PD-MCI patient would be ~75% and ~66% more likely to have an IAF that was below that of a healthy control and a PD-N patient, respectively. If using alpha power for the posterior region, where differences were largest, then a PD-MCI patient would be ~95% and ~80% more likely to have an IAF that was below that of a healthy control and a PD-N patient, respectively. EEG alpha may therefore also be useful to predict future decline associated with cognition in PD. On balance, functional connectivity measures produced smaller differences between groups than did the spectral power measures, although this does not mean that functional connectivity measures might be worse predictors of cognitive change longitudinally.

The evidence for posterior changes for spectral power were confirmed by the significant post-hoc pairwise comparisons between each group and may be attributed to the dual-syndrome hypothesis. This hypothesis is described in Chapter 2, section 2.2, and suggests that posterior cortical function, underpinned by declining cholinergic projections, is associated with cognitive impairment related to progression to PDD. Non-demented PD patients with lower spectral power in the alpha band may have a higher risk of progression to PDD.

8.2 Comparison with the literature

The major strengths of this study were using both (1) resting state and task-based EEG to investigate cognitive decline in PD and (2) by making a direct comparison between PD-N, PD-MCI, and PDD groups, and comparing these to a HC group. The PD-N and PD-MCI participants were classified using Myall et al. (2020) PD-MCI criteria. These

criteria identify PD-MCI patients based on ten neuropsychological tests across five domains, who have a high risk (RR = 8.0) of conversion to PDD within the next four years. As a result, the PD-MCI criteria may be viewed as a proxy of future cognitive decline. Therefore, significant differences between PD-N and PD-MCI may highlight EEG markers of future cognitive decline, even though the current thesis used a cross-sectional design rather than a longitudinal one.

8.2.1 Criteria for classifying PD-MCI and PDD

There have been different perspectives on cognitive impairment and conversion to PDD in the literature. Despite the advent of the MDS criteria for PD-MCI, different methods exist to characterise PD-MCI (J. G. Goldman et al., 2015; Hoogland et al., 2017; Wood et al., 2016). Hoogland et al. (2017) examined the validity of the current MDS criteria as a risk factor PDD. Four studies were included to establish the predictive value of the level II criteria for longitudinal conversion to dementia. They concluded that participants progress to PDD at a much higher rate if they have PD-MCI, which increases as the criterion for the level of impairment increases, but this progression is not always inevitable due to the limitation of not being able to predict a direct generalisation of the results to the individual patient (Hoogland et al., 2017). In a cross-sectional study, J. G. Goldman et al. (2015) investigated the optimal two tests in each of the five cognitive domains to determine a suitable battery of neuropsychological tests that can be used for a PD-MCI diagnosis using the MDS Level II criteria. They did not, however, specify which tests would provide the best diagnostic assessment for longitudinal conversion to PDD. Using a large number of tests, Wood et al. (2016) suggested that the manner in which two test impairments out of 21 measures were conducted influenced the detection of Level II PD-MCI patients who are at risk of PDD over the next four years. This NZBRI study found a relative risk (RR) of 7.2 if the two impairments at -1.5SD below normative data were required within a given cognitive domain, but the RR was 1.7 and nonsignificant when using two -1.5SD impairments only across two domains to identify PD-MCI status in the remaining patients. The NZBRI study by Myall et al. (2020) was not the first to look at relative risk of progression to PDD, but their focus was to identify a limited battery of ten neuropsychological tests (two in each of the five domains to meet Level II criteria) that also have the highest predictive value of

progression to PDD within four years when classifying patients as PD-MCI using -1.5SD as the criterion for impairment. The use of -1.5SD rather than -1SD or -2SD is less likely to capture patients who might revert to a non-MCI status (Saredakis et al., 2019; Wood et al., 2016). They found that RR = 8.0 using this approach, which compares favourably to RR = 6.9 when using full battery of 21 test measures; no restrictions were placed on whether the impairments were within or across cognitive domain in this study. This last approach focused on using sensitive test measures as a way of identifying PD-MCI patients in an efficient manner, but within the primary concept of MCI as a high risk of progression to dementia, rather than the cross-sectional approach taken by J. G. Goldman et al. (2015). In this manner, Myall et al. (2020) obviated the criticism that not all cognitive test impairments reflect risk of progression to PDD (Barker & Williams-Gray, 2014). The use of the new NZBRI criteria (Myall et al., 2020) provided an arguably optimal approach to classify PD-MCI patients in the current cross-sectional EEG study because these patients are clearly at high risk of PDD in the immediate future. In the future it would be good to explicitly compare the current criteria we are using with alternate criteria used in other studies, include alternate neuropsychological tests and thresholds.

Previous oddball task and resting wakefulness EEG studies have used markedly different criteria to characterise cognitive status, albeit sometimes based on the MDS criteria developed by Litvan et al. (2012) (Babiloni et al., 2017b; Babiloni et al., 2018a; Chaturvedi et al., 2019; Hunerli et al., 2019). Unlike the current thesis, however, these prior studies did not use cognitive tests proven to be good independent predictors of progression to PDD. A particular problem is when studies have used only the Montreal Cognitive Assessment (MoCA) or Mini-Mental State Examination (MMSE) scores to characterise PD participants as unimpaired. MMSE scores are not ideal for assessing MCI and may misclassify patients as showing dementia, yet alone cognitive impairment (Burdick et al., 2014; Nieuwenhuis-Mark, 2010). As a result, some studies may have included PD-MCI participants in their PD-N sample, which may be a contributing reason to the difference in findings seen in ERP and resting state EEG studies. Sometimes, the DSM-III or IV has been used to characterise dementia in PD (Fonseca et al., 2013; Fonseca et al., 2009; Han et al., 2013; Hassan et al., 2017; Moazami-Goudarzi et al., 2008; Olde Dubbelink et al., 2013). The MDS criteria for PDD were developed to

counter this problem and have been used in the current thesis, as well as in some previous EEG studies (Caviness et al., 2016; Utianski et al., 2016).

Overall, the results from the studies in this thesis show that some strong EEG effects were found using resting state. By contrast, no differences were found for ERPs using the oddball task. Resting state EEG revealed lower spectral power and functional connectivity in the alpha band and higher spectral power and functional connectivity in the theta band for the PDD group compared to the PD-MCI, PD-N, and HC groups.

8.2.2 Oddball Task

The three-stimulus visual oddball task was first used in this thesis to investigate task difficulty effects in HC and PD-N group. The 'easy' version of the visual oddball task was then used to examine the differences between HC, PD-N, PD-MCI and PDD groups. As mentioned above, there were no differences between groups for amplitude or latency, of either P3a or P3b ERPs, in either study.

The PD literature has reported mixed findings for the amplitude and latency of P3b (i.e. for the target stimulus). Seven ERP studies have made comparisons between a non-demented PD group and a HC group and used either a two-stimulus auditory or a three-stimulus visual oddball task (Bocquillon et al., 2015; Bocquillon et al., 2012; Green et al., 1996; Kaufman et al., 2016; Maidan et al., 2019; Silva Lopes et al., 2014; Wang et al., 1999). Four of these studies reported that P3b latency was prolonged in the PD group compared to the HC group (Kaufman et al., 2016; Maidan et al., 2019; Silva Lopes et al., 2014; Wang et al., 1999). These studies also reported that P3b amplitude was decreased in non-dementing PD participants compared to the HC group. These results contrast with our study's negative findings. However, our findings were consistent with the other three studies did not report any significant differences between the PD and HC group for the P3b latency (Bocquillon et al., 2015; Bocquillon et al., 2012; Green et al., 1996). Two of these studies (Bocquillon et al., 2015; Bocquillon et al., 2012) used the same three-stimulus visual oddball task as our study did, which does not explain the differences between these studies findings and our findings.

Only three studies have made comparisons between HC, PD (non-dementia) and PDD groups (Tachibana et al., 1992; Tanaka et al., 2000; Toda et al., 1993). These studies found no difference for P3b latency between the PD (non-dementia) group and a HC group that used a two-tone auditory oddball task (Tanaka et al., 2000) or a three-stimulus visual oddball task where the probability of seeing the target stimulus was 19% (Toda et al., 1993). However, these studies both found P3b latency was prolonged in PDD participants after presentation of a target stimulus, compared to the PD and HC groups. In regards to the P3b amplitude, prior literature has reported that the P3b amplitude in three-stimulus visual oddball tasks did not differ between HCs and non-demented PD participants (Bocquillon et al., 2012; Gaudreault et al., 2013; Tachibana et al., 1992; Toda et al., 1993; Wang et al., 1999). However, two studies that used a three-stimulus visual oddball task reported a reduction in P3b amplitude for the target stimuli in the non-dementing PD groups, compared to the HC groups (Kaufman et al., 2016; M. Li et al., 2005). Furthermore, no study has investigated group differences using a PD-MCI group in a three-stimulus visual oddball task.

In regards to P3a latency findings, which require three stimuli in the (visual) oddball tasks, all studies except one (Bocquillon et al., 2012; Gaudreault et al., 2013; M. Li et al., 2005; Tachibana et al., 1992; Wang et al., 2000) reported no difference between the non-dementing PD and HC groups after the presentation of a distractor stimulus. These findings concur with those of the current thesis. Only one study has included PD-MCI participants using a two-stimulus visual oddball task (Hunerli et al., 2019). They reported that PD-MCI participants had lower P3a amplitudes than both the HC and non-dementing PD group, and PD-MCI had the longest latency, although this was not significant (Hunerli et al., 2019). For P3a amplitude, two studies reported a reduction in the non-demented PD group in comparison to the HC group, whereas only one study reported no difference in P3b amplitude between a non-demented PD group and a HC group (Kaufman et al., 2016; M. Li et al., 2005; Wang et al., 2000). This differed from our study's findings as there were no reported difference between groups for the P3a amplitude.

The variability in previous studies compared to our study's findings may be a result of contributing factors such as the size and shape of the stimulus, the difference

between the target distractor and standard stimuli, the number of trials, the interstimulus interval, the sample size of each participant group, age, and disease duration of participants, and regions of the brain analysed. Looking at studies that found differences in PD Gaudreault et al. (2013) used various shapes for their target stimulus which consisted of letters that differed at each trial. With respect to the number of trials used, Kaufman et al. (2016) for instance used 600 trials, whereas Toda et al. (1993) used 256-320 trials; our studies used 250 trials for the standard stimulus, and 50 trials for the target and distractor stimuli. Looking at studies that found differences in PD, the age of participants did not appear to have an effect on the findings. Toda et al. (1993) and Tanaka et al. (2000) had on average older PD participants (N = 67.2 years and 65.7 years, respectively), compared to Bocquillon et al. (2012) who had an average of 59.2 for their PD participants. With respect to the PDD participants, studies that reported P3a latency and amplitude differences had younger PDD participants compared to our study. Toda et al. (1993) reported the average age of their PDD participants to be 67.9 years, and the average age of those in Tanaka et al. (2000) was 64.1 years. The average age of our PDD participants was 73.9 years which is significantly older than the above studies. These findings indicate that the age of participants may be a contributing factor as we did not report any significant findings for the P3a and P3b latency and amplitude.

Another point of difference is the sample size in previous studies. Looking at studies that found a difference in PD, the sample size did not appear to influence the findings. With respect to the sample size, our PDD participant group was, on average, a similar size (N = 8) to that of the literature, as Toda et al. (1993) included 9 PDD participants, and Tanaka et al. (2000) had 7 PDD participants. Moreover, the non-demented PD participants groups are mixed in the literature as some had higher participant numbers (N ~ 40) than in our study (N = 19–44) (Bocquillon et al., 2012; Silva Lopes et al., 2014), and other studies had smaller sample sizes (N = ~10) (Bocquillon et al., 2015; Kaufman et al., 2016; Maidan et al., 2019). Similarly, only one study has made a direct comparison between HC, PD-N, PD-MCI, and PDD groups, and this study had a small sample size (HC = 11, PD-N = 29, PD-MCI = 15, PDD = 7), which may have low power and be a reason why they did not identify differences between groups (Tanaka et al., 2000). This may also indicate that our participant groups did not have sufficient statistical power to identify differences between groups as the sample size

was small. Despite some studies reporting clear differences between groups for the P3a amplitude and P3b latency, these mixed findings may be attributed to the reasons listed above and the variability between three-stimulus visual oddball tasks in the literature. Furthermore, the lack of significant differences in our study may be explained by the insufficient difference between the task difficulty of the 'easy' and 'hard' three-stimulus visual oddball task, and the number of trials in the oddball task for both the task difficulty study and the oddball ERP study.

8.2.3 Resting State

Resting wakefulness provides spontaneous EEG measures. The absence of an explicit task is useful when examining individuals with cognitive impairment to determine underlying physiology without the potential confounds of task-related performance, such as fatigue or anxiety. In our cohort, large effects between groups were found for some resting-state EEG measures. The clearest group differences were found for the IAF and spectral power. IAF did not differ significantly between the HC and PD-N group, but progressively decreased for the PD-MCI and PDD groups. Similarly, the spectral power results produced large differences between groups in the alpha and theta bands. The PDD group had the highest spectral power in the theta band, and the lowest spectral power in the alpha band. Spectral power was intermediate for participants with PD-MCI, and lowest in the PD-N and HC group which were similar.

Our results support prior research showing a general trend of lower spectral power and functional connectivity in the alpha band among cognitively-impaired PD patients compared to HCs (Arroyave et al., 2019; Babiloni et al., 2018b; Bosboom et al., 2009b; Caviness et al., 2007; Chaturvedi et al., 2019; Olde Dubbelink et al., 2013; Ponsen et al., 2012; Utianski et al., 2016). With respect to spectral power, three resting-state spectral power studies have made comparison between a non-demented PD group and a PDD group (Bosboom et al., 2006; Fonseca et al., 2013; Ponsen et al., 2012). The first study compared a HC, non-demented PD, and PDD group, using ten regions of interest (Bosboom et al., 2006). They found that in non-demented PD patients, power in the theta band was increased relative to HCs. In PDD patients, there was a decrease in alpha power, relative to the non-demented PD group. The second study made a

comparison between a non-demented PD group and a PDD group using 34 regions of interest (Ponsen et al., 2012). They reported similar findings to (Bosboom et al., 2006), and found that theta power was increased in the PDD group, whereas alpha power was lower for the PDD group, relative to the non-demented PDD group. Spectral power was higher for the PDD group in the delta band compared to a PD (non-demented) and HC groups (Ponsen et al., 2012). Lastly, Fonseca et al. (2013) made comparisons between a non-demented PD, PDD, AD, and HC group using six regions of interest (Frontal left and right, mid temporal left and right, and occipital left and right). They found that the delta and theta spectral power was highest in the PDD group, compared to HCs. Whereas alpha power was highest in the PDD group and lowest in the AD group.

Only one previous study has compared a non-demented PD group with a HC group to investigate spectral power (Han et al., 2013). They did not specify any regions of interest and reported an increase in power in the delta and theta band, and a decrease of power in the alpha band for PD participants, compared to the HCs. Our study suggests that their findings may have depended on a mix of cognitively impaired or non-impaired cases in their "non-dementia" PD group, because PD did not differ from HC for alpha or theta, other than a weak effect for posterior alpha power.

Five EEG resting-state studies have included PD-MCI and PDD participants: three which included PD-MCI and PDD participants, and two which compared PD-MCI and PD participants (Bousleiman et al., 2014; Caviness et al., 2007; Caviness et al., 2016; Chaturvedi et al., 2019; Fonseca et al., 2009). The first study made group comparisons between a PD, PD-MCI, and PDD group, using five regions of interest (anterior, central, occipital, and parietal) (Caviness et al., 2007). They found that PD-MCI exhibited higher delta and theta power and lower alpha power than the non-dementing PD group. However, the PD-MCI and PDD group did not differ significantly in the theta or beta bands. The second two studies made a direct comparison between HC, PD-N, PD-MCI, and PDD group (Caviness et al., 2016; Fonseca et al., 2009). Caviness et al. (2016) did not specify any regions of interest, whereas Fonseca et al. (2009) included a frontotemporal and posterior region. These two studies reported overall that spectral power for the PD-MCI group was higher in the delta band compared to the PD-N group and the PDD and PD-MCI did not differ in the theta or beta bands, but

PDD had higher delta and lower alpha band power than the PD-MCI group (Caviness et al., 2016; Fonseca et al., 2009). Overall, the trend in the literature has been for lower spectral power in the alpha band and higher spectral power in the theta band for PD-MCI and PDD participants, with the PD-MCI for both bands being an intermediate value between the PD-N and PDD group. These findings correspond to our study and indicate that cognitive decline has a relatively robust association with EEG measures irrespective of the measures used for spectral power.

As outlined above, the current functional connectivity literature also follows the same general trend of lower functional connectivity in the alpha band, and higher functional connectivity in the theta band for PDD patients compared to HCs (Bosboom et al., 2009b; Chaturvedi et al., 2019; Geraedts et al., 2018b; Ponsen et al., 2012; Utianski et al., 2016). There are two studies that made comparisons between a non-demented PD group and a HC group (Moazami-Goudarzi et al., 2008; Olde Dubbelink et al., 2013). These studies both reported an increase in the theta band, and a decrease in the alpha, for the PD group compared to the HC group. Moazami-Goudarzi et al. (2008) also found the increase in the theta band in the anterior region, and the decrease was found in the posterior. Two other studies have compared PDD and non-demented PD groups and reported that the PDD group had higher functional connectivity in the theta band and lower functional connectivity in the alpha band (Bertrand et al., 2016; Bosboom et al., 2009b; Ponsen et al., 2012). These studies made a comparison between a non-demented PD and a PDD group and found that compared to the non-demented PD participants, PDD participants had more delta and theta power. They also reported that the PDD participants had lower functional connectivity in the alpha band, especially in the parieto-temporo-occipital region. Bosboom et al. (2009b) used coherence as their functional connectivity measure, whereas Ponsen et al. (2012) used PLI. These significant group differences in the alpha band suggest that specific disruptions of brain communication may be measured before PD patients develop dementia, and potentially provide a new marker to identify patients at highest risk of developing dementia (Bertrand et al., 2016). However, the spectral power findings in the posterior region for the alpha band may be a stronger separator of cognitive groups due to the significant differences between each pairwise comparison.

Five studies have included PD-MCI participants in their investigation of functional connectivity (Arroyave et al., 2019; Babiloni et al., 2018b; Chaturvedi et al., 2019; Hassan et al., 2017; Utianski et al., 2016). These studies reported that their PD-MCI groups had lower functional connectivity in the alpha band compared to the non-dementing PD and HC groups (Babiloni et al., 2018a; Hassan et al., 2017). These studies also found no significant differences in functional connectivity between the non-dementing PD and HC group, which aligns with our findings. Hassan et al. (2017) made comparisons between non-demented PD, PD-MCI, and PDD groups, using 68 regions of interest, and PLI as their functional connectivity measure. Furthermore, Babiloni et al. (2018b) compared HC, AD-MCI, and PDD groups, used five regions of interest (anterior, central, parietal, occipital, and temporal), and coherence as their measure of functional connectivity. These two studies reported the same findings which suggests different measures of functional connectivity measure do not substantially influence results. In contrast, Arroyave et al. (2019) compared HC, non-demented PD, and PD-MCI groups and reported that their PD-MCI group had higher functional connectivity in the alpha band compared to the PD-N group, which differs from the other PD-MCI functional connectivity studies. Their study used 8 regions of interest and classified their PD participants using the MDS Level I criteria, which differs from our study which used the NZBRI PD-MCI criteria. They suggested that their results may be due to their categorisation of participants and previous literature not separating PD patients with MCI as a separate group (Arroyave et al., 2019). Other studies, including Chaturvedi et al. (2019) used ten regions of interest, and compared a PD group, and a PD-MCI group. Participants were classified using the MDS Level II criteria for PD-MCI and their study reported lower functional connectivity in the PD-MCI group compared to the HCs in the beta band, and higher functional connectivity for the PD-MCI group in the theta band compared to their PD-N group (Chaturvedi et al., 2019).

However, only one resting-state functional connectivity study has made a direct comparison between HC, PD-N, PD-MCI, and PDD (Utianski et al., 2016). Their study included PD-MCI participants and reported overall that functional connectivity for the PD-MCI group was higher in the delta band compared to the PD-N group and the PD-MCI and PDD group also had lower alpha functional connectivity than the PD-N group. They also reported that functional connectivity in the theta band was higher in their PD-

N group compared to their HC group. These findings differ slightly from our study as the PD-MCI group did not differ significantly from the PD-N and PDD group. These differences may be due to the variety of classification criteria used in the literature for PD-MCI. These differences in the theta band especially may be due to the multiple functional connectivity measures to analyse the data. This perhaps indicates that different functional connectivity measures may provide different patterns of results for PD. These differences also illustrate that there are two types of MCI, which are classified depending on which criteria is used. Both criteria have PD-MCI but one has high risk of progression to PDD within four years (Myall et al., 2020), and the other does not (Litvan et al., 2012).

The differences between previous studies may be due to the methodological variability between functional connectivity and spectral power measures such as the sample size, disease duration, and brain regions of interest. Looking at a spectral power study that found differences in PD, they have included a range of sample sizes for participant groups which does not appear to influence the findings. Fonseca et al. (2009) made a direct comparison between a HC (N = 26), PD-N (N = 15), PD-MCI (N = 10) and PDD (N = 7) group that had smaller sample sizes than our sample (HC = 29, PD-N = 44, PD-MCI = 40, PDD = 12), despite finding similar results for spectral power. This may indicate that the larger sample sizes provide more confidence in the findings. Functional connectivity studies had larger sample sizes for the PDD groups (N ~ 18) in comparison to the sample sizes our study used (Bertrand et al., 2016; Ponsen et al., 2012). There have also been variations in the resting state, as previous studies have investigated eyes-closed resting state as well as eyes-open resting state (Bosboom et al., 2006; Fonseca et al., 2009; Ponsen et al., 2012). Ponsen et al. (2012) used both an eyes-closed and eyes-open resting state and reported lower functional connectivity values in the fronto-temporal and parieto-temporo-occipital which differs from our studies that reported no difference between groups in the delta band. Using an eyes-open resting-state condition may contribute to differences in the literature as our study only used an eyes-closed resting-state session. Therefore, future work could investigate the differences between eyes-closed resting and eyes-open resting wakefulness in PD.

A range of brain regions have also been used to look at spectral power and functional connectivity group differences. In the literature, the posterior regions may include both parietal and occipital electrodes (Bertrand et al., 2016; Moazami-Goudarzi et al., 2008; Teramoto et al., 2016), whereas some studies have examined parietal and occipital regions separately, making direct comparisons across regions not possible in some cases. However, the classification of regions did not explain the difference between Arroyave et al. (2019), who found that their PD-MCI group had higher functional connectivity in the alpha band compared to the PD-N group. Whereas Chaturvedi et al. (2019) found that their PD-MCI group had lower functional connectivity in the alpha band compared to the PD-N group. Both of these studies used the same regions of interest, (left and right for the anterior, central, parietal, temporal, and occipital). Other brain regions commonly compared in the literature are the anterior and central region, and some studies have included the temporal regions into their anterior regions and classified them as fronto-temporal regions (Bosboom et al., 2009b; Caviness et al., 2007). However, this classification did not explain the difference in findings between Bosboom et al. (2009b) and Caviness et al. (2007) who both reported that despite the regions of interest differing between studies, they found that the PD-MCI exhibited higher theta power compared to the PD-N group. Despite the regions of interest differing between studies, these findings indicate that regions of interest do not appear to be a contributing factor.

Another point of difference in the resting-state spectral power and functional connectivity literature could be clinical and demographic issues in PD, including the disease duration of participants. Looking at studies that found differences in PD found that the disease duration varied in the literature as many of the non-dementing PD participants were early on in the disease (4.0–9.7 years) (Arroyave et al., 2019; Caviness et al., 2007; Chaturvedi et al., 2019; Ponsen et al., 2012; Teramoto et al., 2016) which is lower than our PD-N participants (9.7 years). Moreover, these differences in disease duration in comparison to our participants (PD-N = 9.7 years) do not explain the differences between studies, and an effect was found regardless of participants disease duration.

Lastly, all previous functional connectivity PD studies have used PLI or coherence as their analysis measure (Arroyave et al., 2019; Babiloni et al., 2018b; Bertrand et al., 2016; Bosboom et al., 2009b; Chaturvedi et al., 2019; Geraedts et al., 2018b; Hassan et al., 2017; Lau et al., 2012; Mehraram et al., 2020; Moazami-Goudarzi et al., 2008; Olde Dubbelink et al., 2013; Ponsen et al., 2012; Teramoto et al., 2016; Utianski et al., 2016; Vinck et al., 2011). However, the findings did not differ substantially between the functional connectivity measures used in our study and those in the literature, but our findings reported larger effects despite similar patterns overall. PLI and coherence have constraints associated with them, as outlined in Chapter 3, section 3.3.2. Our study used the dwPLI measure to reduce the common issue of volume conduction. This suggests that cognitive decline has a relatively robust association with EEG measures, irrespective of the functional connectivity measures used.

8.3 Implications for Parkinson's disease

As outlined, PD is a degenerative disorder which shows diversity in the severity and breadth of neuropathology and in particular variation across patients in terms of cognitive decline and progression to PDD (Kehagia et al., 2013). Although abnormal alpha-synuclein is the defining feature of PD (Kehagia et al., 2013), the varied mechanisms that cause degeneration in the brain are not fully understood. Various patterns of cognitive-relevant degeneration exist, one of which is described by way of the dual-syndrome hypothesis (Gratwicke et al., 2015). This hypothesis suggests that posterior cortical function, and underpinned by declining cholinergic projections, is associated with progression to PDD (Gratwicke et al., 2015; Kehagia et al., 2013). In the current study, spectral power and group differences were generally seen posteriorly, which is consistent with the dual syndrome hypothesis in terms of progression to PDD.

There are multiple explanations which attempt to explain the EEG changes that correlate with cognitive status in PD. It has been theorised that an increase in theta activity is believed to represent dysfunction in diffuse gray matter areas in both cortical and subcortical areas (Caviness et al., 2007). Babiloni et al. (2017a) also suggest that functional connectivity changes could be attributed to impairment of the cortical gray matter especially in the posterior regions of the brain. If so, EEG studies in the future

need to be complemented in the future by parallel evidence on measures of MRI structure and function of the brain.

Other studies suggest that worsening performance on working memory and rule-switching tests, which require attentional resources, could reflect changes in attentional executive function networks in patients with PDD (Gratwicke et al., 2015). However, due to time constraints, this project examined correlations with the global cognitive Z-score rather than individual tests that may be more related to memory and attention. Future research could look at individual scores and EEG measures.

Our findings for both the task difficulty ERPs ('easy' vs 'hard'), and the 'easy' task ERPs did not find any group differences for the P3a and P3b amplitude and latency. By contrast, a previous review of event-related-potentials and cognition in PD, by Seer et al. (2016), suggest that cognitive ERPs in PD exist that can be interpreted within the dual-syndrome perspective of cognitive dysfunction in PD. Therefore, P3a may be related to fronto-striatal dysfunction that is not associated with decline to PDD and P3b may be associated with global cognitive impairment and progression to PDD. This is reiterated by Seer et al. (2016) who has suggested that prolonged latency in the PDD group compared to the HC group is due to the duration of stimulus evaluation being prolonged and that this is not a result of PD-specific neurodegeneration, i.e. from nigrostriatal dopamine depletion (Seer et al., 2016). Our results from both ERP studies concluded that the ERP measures did not change in PD, irrespective of whether patients were PD-N, PD-MCI or PDD. Furthermore, P3b amplitude trends that showed non-significant evidence for the PD-N participants in the parietal region for the target stimulus may indicate the higher attentional resources being deployed by these participants to compensate for their awareness of the degeneration happening in the brain, as suggested by Green et al. (1996). They suggested that inefficiency in brain function due to PD required patients to devote extra attentional resources to the oddball task in order to achieve high performance on the task (Green et al., 1996). This may have only occurred in the PD-N group as initial compensation was deployed by these participants but is lost by the time cognitive decline occurs.

8.4 Critique

A key limitation, as mentioned in previous chapters, was the small sample size for the PDD participants (sample size of 15-17 patients across analyses). The PDD group was harder to recruit mainly due to the severity of cognitive decline and the inability for these participants to physically attend the session. This is due to majority of PDD participants being relatively fragile, often residing in care facilities and unable to attend an EEG lab without a caregiver or significant other providing assistance for travel. Some PDD participants were unable to complete the task as they could not understand the instructions or were not able to react within the time limit of 2 s after the presentation of the stimuli on screen and had to be excluded. Nonetheless, including the PDD patients in the analysis provided a novel contribution to the literature, as previous literature examining patients with PDD is limited, especially with respect to using a three-stimulus visual oddball task (Tanaka et al., 2000; Toda et al., 1993). Previous studies on resting-state spectral power and functional connectivity studies, however, had a mix of sample sizes that were both small and larger for the PDD group, in comparison to our study. These PDD sample sizes ranged from (N = 7-31) (Bertrand et al., 2016; Bosboom et al., 2009b; Caviness et al., 2007; Caviness et al., 2016; Fonseca et al., 2013; Fonseca et al., 2009; Ponsen et al., 2012; Utianski et al., 2016), whereas our sample size for the spectral power and functional connectivity study was (N = 12). The studies mentioned above all reported higher spectral power and functional connectivity for their PDD group compared to the HC group, and lower alpha spectral power and functional connectivity compared to their HC group. Furthermore, these findings mirror what we found in our smaller cohort of patients and suggests that the sample size does not influence the significance of the findings.

Aside from the small sample size of PDD patients, another limitation of this study was the older sample for HC participants. The age difference between the HC and PD participants was approximately 10 years which is significant, however the results determined that age did not affect the conclusions, at least in terms of being accounted for by the covariate analyses. For the recruitment of these participants, we used a convenience sample which resulted in the HC's being older due to majority of the participants being retired and having the time to participant in the study whereas people who

are working are not as able to participate and complete the study. In future, including HC participants that are younger would be ideal to ensure that there are no differences between groups which can be attributed to age.

Another limitation of our studies concerns the methodology employed to conduct the resting-wakefulness EEG session (Chapters 6 and 7). Initially participants were required to engage in a ten-minute resting wakefulness paradigm and remain awake throughout the period. It was, however, realized upon initial processing of the data that participants could sometimes become a drowsy and some even fell asleep. This meant we excluded participants who did not have at least 180 s of artefact-free epochs. Thirty-two participants completed the ten-minute uninterrupted resting state, although these participants were HCs and PD-N participants which are less likely to fall asleep due to their age and cognitive status. Most of these participants were able to be included in the final analysis as they had 180 s of usable data. The remaining participants (N = 134) completed the resting-state using the protocol of waking the participant periodically every three minutes in addition to closer inspection throughout. We consequently devised a new approach to optimise the resting-wakefulness paradigm and ensure that participants were not drifting into sleep. The new approach modified the original ten-minute resting wakefulness session and was divided it into three epochs of three minutes each with an explicit brief interruption between each epoch. This was to ensure the participant remained awake and to minimise drowsiness. Fortunately, this change was implemented immediately to improve the resting wakefulness session.

A limitation in the ERP studies was the number of stimuli presented for each three-stimulus oddball task (Chapter 4 and 5). Each task included 50 target stimuli, 50 distractor stimuli, and 500 standard stimuli. When the data were analysed, all epochs that had movement artefacts or incorrect responses were removed and only correct response trials were retained, as per usual practice in this field. This led to a significant portion of trials being removed and N = 16 participants being excluded from analysis (N = 4 from the task difficulty analysis, and N = 12 from the ‘easy’ oddball analysis). The practice task currently requires the participant to correctly identify at least 70% of the target stimuli, and correctly reject at least 70% of the standard stimuli, in order to proceed to the main task. Future studies could require participants to complete the task

until they correctly identify a specific number of targets, similar to the practice task, but would need to be limited to avoid fatigue. It would also be valuable to increase the number of trials in total to increase the number that can be included in an analysis. However, this would also need to avoid fatiguing some patients. If the primary goal is to examine the effects of cognitive decline, then the more standard two-stimulus task could be used which would immediately increase the total number of trials available as well as simplify the instructions for participants.

8.5 Future Directions

Perhaps by using a two-stimulus oddball task, future work could explore the relationship between cognitive decline and task difficulty in more detail, as this is an unexplored area of PD research. Using a simpler base task may allow three levels of difficulty to be used to allow the addition of participants with cognitive impairment in PD (i.e., PD-MCI and PDD). Having these groups included in the analysis may help to determine ERP markers for those at higher risk of progression to PDD.

Results chapters (Chapters 4-7) included effect sizes for key comparisons. These effect sizes outlined the strength of group differences on specific measures. However, effect sizes could also be examined using the non-parametric measure of area under the curve (AUC), which would better specify the ability of a measure to discriminate between pairs of groups or indeed across three ordinal groups, as has been done for the MoCA and MMSE (Dalrymple-Alford et al., 2010). Pairwise differences in AUC function could then be examined to determine the relative utility of different EEG measures in discriminating groups.

In Chapter 6, we demonstrated that posterior group differences in the alpha band power were indicative of markers that discriminated all three PD groups and, by inference, progression to PDD. As mentioned previously, the specific PD-MCI criteria we used reinforce the idea that the three groups reflect progression that might be expected in individuals over time, albeit inferior to a longitudinal follow-up. This measure is a relatively strong predictor of cognitive decline as spectral power for the HC group was highest in the alpha band and decreased substantially for the PD-MCI and PDD groups.

A future direction would be to use a more general model of prediction for individual patients, rather than group-level analyses. These could use leave-one-subject-out cross-validation for classifier training and for estimation of classifier accuracy of what would be achieved with an independent subject. Leave-one-subject-out cross-validation is less common and relatively new in the context of spectral power and functional connectivity PD literature. This method trains a model based on all the data except for one subject, therefore making a prediction for the ‘left-out’ patient, and then cycles through

all the patients in the same manner. This and other types of machine learning have not been fully explored using EEG measures in PD. Using functional connectivity and spectral power as a method of analysis would provide (1) more informative functional connectivity and spectral power data and (2) additional information about the role of progression to PDD in the patients currently in our study, which is part of the longitudinal PD research programme at the NZBRI. Longitudinal changes can be measured at the group level. This is of substantial value but, even more so, will be prediction of progression in individual patients by way of a predictive classifier trained via leave-one-subject-out machine learning.

Functional connectivity has been used in the past in both our study and previous literature to determine spectral and regional differences in PD (Bosboom et al., 2009a; Ponsen et al., 2012; Utianski et al., 2016). However, even though this research has provided us with a deeper understanding of functional connectivity differences in PD, it is not directional. Functional connectivity is used to measure the strength of connections between brain regions and uses the information available to identify interdependence between activity of electrodes but does not exploit prediction in time to infer effective (i.e. directional) connectivity (Stephan et al., 2009). Further exploration could include functional connectivity for ERP measures in the oddball task. Functional connectivity has not been investigated in an oddball task, and this might help to determine the difference between patients who develop PDD at a faster rate compared to those who remained dementia-free for a prolonged period. Investigating effective connectivity in resting wakefulness as well as in a visual oddball paradigm would be another future direction to expand on our findings and determine the specific nature of functionality in the brain. By doing this, identification of the process of degeneration could be explored further by investigating posterior ERP and frequency band group differences in PD-MCI and PDD participants. This would help to determine whether or not degeneration in the posterior region of the brain is strongly associated with cognitive impairment related to progression to PDD (Kehagia et al., 2013).

8.6 Concluding Remarks

Using spontaneous resting state EEG measures are valuable tools to discriminate cognitive status in PD, at least at the group level. They may also be useful to track progression and the efficacy, of disease-modifying interventions. In this thesis, we were the first to examine oddball task difficulty in a sample of PD-N patients, that is not meeting criteria for PD-MCI, although no effects were found for the P3a and P3b latency or amplitude. When the 'easy' task was used to compare HC, PD-N, PD-MCI, and PDD groups, there were again no significant group differences for the P3a and P3b latency or amplitude.

In the resting state, decline in IAF was associated with PD-MCI status, but worsened with a PDD status. Furthermore, spectral power was highest in the theta band and lowest in the alpha band for the PDD group. Group differences in alpha power were evident in the posterior brain region, smaller in the central region, but not evident the anterior brain region. For the posterior region, alpha power was highest in the HC group and decreased linearly across PD-N, PD-MCI and PDD groups. Spectral power in the theta band was intermediate in the PD-MCI group compared to the PDD group and the PD-N and HC groups; the latter two groups had similar theta power. We were also the first to use the dwPLI to calculate functional connectivity in resting-state. We have shown that functional connectivity displayed similar trends but the PD-MCI in general was closer to the PD-N group and not as intermediate as in the spectral power results. These studies provided a promising endeavour into resting state and task-related EEG measures across the full spectrum of cognition, and have the implications of developing biomarkers for future cognitive decline in PD.

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