

**Understanding the temporal dynamics of
visual hallucinations in Parkinson's disease
with dementia**



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Abstract

Background

Integrative models of visual hallucinations (VH) posit that the symptom requires disruptions to both bottom-up and top-down visual processing. Although many lines of evidence point to a mixture of aberrant processing and disconnection between key nodes in the visual system, in particular the dorsal and ventral attention networks, there have been no attempts to understand the dynamic behaviour of these systems in Parkinson's disease with dementia (PDD) with VH.

Aims

The primary aim of this thesis was to explore the correlates of synaptic communication in the visual system and how spatio-temporal dynamics of the early visual system are altered in relation to the severity of VH. The secondary aim was to help understand the balance between the contributions of bottom-up and top-down processing for the experience of VH in PDD.

Methods

An assortment of investigative approaches, including resting state electroencephalography (EEG), visual evoked potentials (VEPs), and concurrent EEG and transcranial magnetic stimulation (TMS) were applied in a group of PDD patients with a range of VH severities ($n = 26$) and contrasted with a group of age matched healthy controls ($n = 17$).

Results

Latency of the N1 component was similar between groups, suggesting intact transfer between the retina and the cortex. However, PDD patients had an inherent reduction in the amplitude of the VEP components and displayed a pattern of declining P1 latencies in association with more frequent and severe VH. Evoked potentials arising from TMS of the striate cortex were similar in amplitude and latency for each of the components between PDD and controls. However, inter-component activity at several stages was altered in the PDD group, whilst the frequency and severity of VH was positively associated with the amplitudes of several components in the occipital and parietal regions. Finally, attentional modulation as measured by the alpha-band reactivity was also compromised in PDD patients.

Conclusions

These data provide neurophysiological evidence that both early bottom-up and top-down dysfunctions of the visual system occur in PDD patients who hallucinate, thus supporting integrative models of VH.

*For the world,
I hope this helps.*

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This has not been an easy ride. The time spent working towards the completion of this PhD has been one of the most stimulating, exciting, and fulfilling experiences of my life. I have gained valuable knowledge and skills, and hopefully contributed to the knowledge and skills of others in the process. From this experience I have learned far more about myself and the world around me than I ever could have imagined at the start of this journey, which greatly outweighs the cost of my achievements.

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List of Abbreviations

AD – Alzheimer’s disease

AGCL – Silver chloride

ANCOVA – Analysis of covariance

ASA-LAB – Advanced source analysis laboratory

BOLD – Blood oxygen level dependent

BPP – Bistable perception paradigm

BSS – Blind source separation

CAF – Clinician assessment of confusion and quality of consciousness test

CAMCOG – Cambridge cognitive test battery

ChI – Cholinesterase inhibitors

CI – Confidence interval

CNV – Contingent negative variation

DAN – Dorsal attention network

DLB – Dementia with Lewy bodies

DMN – Default mode network

EEG – Electroencephalography

EMD – Empirical mode decomposition

EMG – Electromyography

ERG – Electroretinography

ERP – Event related potential

FFT – Fast Fourier transform

fMRI – Functional magnetic resonance imaging

GFP – Global field power

HP – Hewlett Packard

IAPF – Individual alpha peak frequency

ICA – Independent components analysis

IMF – Intrinsic mode function

LBD - Lewy body dementia

LGN – Lateral geniculate nucleus

LOGMAR – Logarithm of the minimum angle of resolution

LRP - Lewy related pathology

MMSE – Mini mental state exam

MOCA - Montreal Cognitive Assessment

MS – Multiple sclerosis

MWU – Mann-Whitney U

N1 - First negative component in the visual evoked potential waveform

N2 - Second negative component in the visual evoked potential waveform

NBM – Nucleus Basalis of Meynert

NEVHI – North East Visual Hallucinations Interview

NPI – Neuropsychiatric Inventory

P1- First positive component in the visual evoked potential waveform

PAD – Perception Attention Deficit model

PC – Phosphene complexity

PD – Parkinson’s disease

PDD - Parkinson’s disease with dementia

PD-MCI – PD mild cognitive impairment

PN – Processing Negativity

PSD – Power spectral density

PT – Phosphene threshold

REM – Rapid eye movement

ROI – Region of interest

rTMS – Repetitive TMS

SI - Stimulation intensity

TEP – TMS evoked potential

TMS - Transcranial magnetic current stimulation

TUHARS – Tottori University Hallucinations Rating Scale

UPDRS – Unified Parkinson’s disease rating scale

VAN – Ventral attention network

VEEGStim - Visual hallucinations: an EEG and non-invasive stimulation study

VEP – Visual evoked potential

VH – Visual hallucinations

Chapter 1 Introduction

"Woe to you, oh earth and sea, for the devil sends the beast with wrath, because he knows the time is short...." – The Number of the Beast, Harris, S. (1982)

1.1 Overview of Parkinson's disease with Dementia

Parkinson's disease with dementia (PDD) belongs to a class of neurodegenerative dementias primarily characterised by the presence of Lewy bodies (LBD), which are small aggregates of the protein alpha-synuclein and also ubiquitin that form in the pre-synapse of neo-cortical, sub-cortical, and brainstem neurons (McKeith et al, 2005; Braak et al, 2003; Emre, 2007; Schulz-Schaeffer, 2010). Disease progress is also associated with a depletion in the density of cholinergic (Francis et al, 2007; Perry et al, 1985; Perry et al, 1980; Dubois et al, 1983), monoaminergic (Scatton et al, 1983), and dopaminergic neurons (Braak et al, 2003; Javoy-Agid et al, 1981; Mortimer et al, 1982; Scatton et al, 1982), further impairing the control of executive attention and cortico-cortical, as well as cortico-muscular communication.

The cognitive profile associated with PDD includes dysexecutive function, visuo-perceptual impairment, disrupted language comprehension and communication and memory loss (Mosimann et al, 2004; Urwyler et al, 2014; Emre et al, 2007; McKeith et al, 1996; McKeith et al, 2005). The worsening of the cognitive profile is associated with increased disease duration and age (Hughes et al, 2000; Aarsland & Kurz et al, 2010) which in turn predict the development of more severe neuropsychiatric symptoms, in particular, that of complex recurrent visual hallucinations (VH). The development of VH is related to increased patient and caregiver distress (Factor et al, 2003), and subsequently a greater risk of nursing home placement (Goetz et al, 1993; Goetz et al, 1995). Despite this particular symptom carrying strong implications for quality of life the aetiology of VH in PDD is little understood, thus limiting the scope for effective treatment and management.

1.2 Epidemiology of PDD

The incidence of dementia in PD has previously been estimated at 2.5 per 100,000 person years, with an increase up to 47 in patients between 80 and 99 years of age (Savica et al, 2013; Hely et al, 2008). Irrespective of age the progression of PD towards a dementia syndrome is a significant predictor of increased mortality (Levy et al, 2002; Emre et al, 2007),

leading several recent investigations to conclude that the prevalence of dementia in the PD population is often under-represented (Aarsland et al, 2005; Rijk et al, 1997). When not controlling for mortality related attrition longitudinal studies performed over periods of up to 20 years have described a prevalence of dementia between 60% and 75% in community based cohorts (Hely et al, 2008). Further, cumulative prevalence increases to a maximum of 90% as the surviving patients reached 90 years of age (Buter et al, 2008). The risk of developing dementia is further predicted to rise up to four fold in the presence of mild cognitive impairment (Pederson et al, 2013; Baba et al, 2012), VH (Marion et al, 2008), rapid eye movement (REM) sleep behaviour disorder (Haugarvoll et al, 2005), and up to 20-fold in the presence of olfactory disturbances (Marion et al, 2008). Thus in the majority of patients with PD there appears to be a progressive neurodegenerative process which extends well beyond causing motor symptoms and this has significant ramifications for patients in terms of prognosis and future quality of life.

1.3 General Pathology and Pathogenesis

At a neuronal level, over the course of time PD evolves beyond a simple disruption of the motor-dopaminergic system, eventually manifesting as a wide spread disruption of local and inter-cortical communication affecting the processes involved in executive control, visual perception, and emotion (Brønneck, 2015). Based on the Braak staging hypothesis (Braak et al, 2003) the development of dementia is believed to begin during the transition of Lewy related pathology (LRP) from the brainstem to include the limbic system and the neo-cortex, then as the LRP burden increases in cortical regions the severity of cognitive symptoms is also shown to increase (e.g. Harding et al, 2002). This is possibly due, in part, to synaptic dysfunction relating to the aggregation of alpha synuclein within the pre-synapse (Schulz-Schaeffer, 2010), but likely to represent a mechanism of dysfunction in tandem with the depletion of cholinergic (Perry et al, 1995) and dopaminergic (Mortimer et al, 1982; Bosboom et al, 2006) neurons, although other neurotransmitter systems (e.g. noradrenergic, serotonergic) which have been less studied may also have a role (Emre, 2003; Bosboom et al, 2006).

The disruption of the dopaminergic system is classically associated with the motor system disturbances reported in PD (Mortimer et al, 1982), whereas the depletion of noradrenergic and serotonergic neurons is linked to mood-disorders such as depression and anxiety (Weintraub et al, 2003; Richard et al, 1997). However, beyond the dopaminergic motor system disturbances the primary neuropathological disruption is to the cholinergic system, following the lesioning of tracts ascending from the nucleus basalis of Meynert (NBM; Braak

et al, 2003; Gratwicke et al, 2013; Francis et al, 2007; Bohnen et al, 2011). This change occurs early on during stage three, referred to as the transitional period, in the Braak model of Lewy body progression (Braak et al, 2003), and has been correlated with decline in executive control (Bohnen et al, 2006; Kehagia et al, 2010; Yarnall et al, 2011; Ravina et al, 2005), as well as the occurrence of complex VH (Bosboom et al, 2009; McKeith et al, 2004; Perry et al, 1990).

The mechanism by which Lewy body pathology spreads from the brainstem towards the neo-cortex is still widely debated, and speculation upon this mechanism is beyond the scope of this investigation. However, a number of sources have considered the possibility of inflammation (Whitton, 2007; McGeer et al, 1988), oxidative stress (Jenner, 2003), and a prion-like spread (Schulz-Schaeffer, 2010; Braak et al, 2008). However, with cellular mechanistic theories mostly derived from mouse models (e.g. Masuda-Suzukake et al, 2013) there is a limited knowledge base about how this translates to the human brain. Thus it is equally as plausible to presume that alpha synuclein aggregates form in response to other elements of the neurodegenerative process as a neuroprotective factor (Revuelta et al, 2015). A much greater body of work is still required to answer this question.

1.4 Cognitive Profile

The cognitive profile associated with PDD is primarily a dysexecutive syndrome, although memory and visual perception, as well as mood regulation and language are also affected with an annual decline in global cognitive performance similar to that seen in Alzheimer's disease (AD; 2.3 points on the mini mental state exam [MMSE], compared to one point in non-demented PD; Emre et al, 2007; Aarsland et al, 2004). Unlike AD the spread of pathology does not result in widespread loss of cortical or subcortical matter, instead factors affecting the density and efficiency of neuron synapses are likely to be important in influencing the flow and control of neuronal communication. As such the transition into a dementia syndrome can be predicted by performance on global executive functioning (e.g. stroop task performance, Janvin et al, 2005; total MOCA score, Hu et al, 2014; semantic and verbal fluency, Lambon-Ralph et al, 2001), visual attention (e.g. object orientation, Hu et al, 2014), and memory tasks (Levy et al, 2002) at baseline. In addition to poor executive performance dementia in PD is further characterised by fluctuating cognition (Metzler-Baddely, 2007; McKeith et al, 2005; Emre et al, 2007); this is typically measured by the clinician based on the carers reports of consciousness and confusion in the month prior to the meeting (Walker et al, 2000), but have also been studied using lab measures of attention such as simple reaction time, choice reaction time and digit vigilance (e.g. Ballard et al, 2002). In this particular

measure 29% of the PDD group, compared with 42% of the DLB group and only 4% of the control group, presented with noticeable fluctuations in cognition (Ballard et al, 2002).

Memory is significantly impaired in PDD compared to healthy controls (Brønneck, 2015), however, despite the general similarity in memory impairments between PDD and AD (Metzler-Baddeley, 2007) the profile of memory deficits is qualitatively different between the two (Litvan et al, 1991), and different still from PD without dementia, where subtle memory deficits can be evidenced (Lehrner et al, 2015; Pfeiffer et al, 2014; Burdick et al, 2014; Winder-Rhodes et al, 2015). Whilst AD is characterised by more amnesic damage, working memory, and recognition deficits (Noe et al, 2004), memory in PDD is more likely to show deficiencies in visual (Noe et al, 2004; Cormack et al, 2004) and verbal (Levy et al, 2002; Troyer et al, 1998) memory. Nevertheless, akin to AD, PDD memory impairments in the later stage appear to suffer from a mixture of encoding and retrieval problems as shown by failure to improve in recall performance when provided with cues (Higginson et al, 2005). This possibly reflects a combination of LRP burden and elevated levels of AD related Tau pathology (Dickson et al, 2015; Ferman et al, 2015; Gomperts et al, 2015).

1.5 Visual Perception

1.5.1 Non-Cortical

In both PD and PDD often the earliest signs of visual disturbances are double vision, dry or painful eyes, poor contrast sensitivity, problems with colour vision, and the blurring of vision or lowered acuity (Archibald et al, 2009; Urwyler et al, 2014; Biousse et al, 2004; Davidsdottir et al, 2005). Although the integrity of the retina will gradually diminish with age, comparisons of PDD and age matched controls demonstrate strong patterns of impairment associated with PDD, dissociating the above complaints from age related degeneration (Archibald et al, 2009). Post-mortem study of the eyes in patients who had lived with PD demonstrates that the gross structure, which might affect the passage of light through the eye (e.g. density of vitreous humour) was similar to that of healthy controls irrespective of hallucination status (Kopal et al, 2015); whereas the finding of pale inclusions (Maurage et al, 2003), and reduced retinal dopamine (Nguyen-Legros, 1988), as well as retinal nerve fibre layer thinning (Lee et al, 2014) provides evidence of disturbed cellular communication and transmission of information away from the retina; however, there is still strong debate concerning the precise role of the latter in visual perceptual dysfunctions (e.g. Yamamoto et al, 2006; Erskine et al, 2015; Lee et al, 2014) and this is discussed in greater detail below (**section 1.10.3**). These findings are supported by electrophysiological studies using visual

evoked potentials (Bodis-Wollner & Yahr, 1978; Regan & Neima, 1984; Nightingale et al, 1996; Murphy et al, 2015) and electroretinogram recordings (Nowacka et al, 2015; Nightingale, 1986; Gottlob et al, 1987) which demonstrate diminished retinal outputs, notably reductions in waveform component amplitudes (this is discussed in greater detail below). The implied relationship between these findings and the density of dopamine cells in the retina is further reinforced by improvements in the electrophysiological response towards control-like characteristics after the administration of levodopa (e.g. Peppe et al, 1995; Onofrj et al, 1986).

1.5.2 Cortical

Although the visual complaints described above will undoubtedly be exacerbated by alterations in processing at the cortical level it is clear that they have an origin in retinal pathology (Archibald et al, 2009). However, numerous imaging reports display structural (e.g. volume reduction) and physiological (e.g. blood oxygen level dependent response, BOLD) changes within the dorsal and ventral visual streams (Burton et al, 2004; Colloby et al, 2002; Harding et al, 2002; Goldman et al, 2014; Boecker et al, 2007), corroborated by neuropsychological reports of impaired visuo-perceptual/spatial ability (e.g. visual search, object form perception; motion discrimination; angle discrimination; and praxis as measured using pentagram copying; Mosimann et al, 2004; Yokoi et al, 2014) when compared to controls and AD. Often these are more pronounced in PDD than in non-demented PD, and further impaired in patients who experience recurrent complex VH (Mosimann et al, 2004). Based on the profile of executive functioning it is unsurprising that tasks requiring discrimination or goal directed visual behaviour are impaired in PDD, implying that a large proportion of problems with visual perception are based on the distribution of pathology affecting communicative pathways such as the cholinergic and dopaminergic systems; problems with visual spatial cognition, such as mental object rotation, bi-stable perception, angle discrimination, and visual counting (Archibald et al, 2013; Metzler-Baddeley et al, 2010; Boller et al, 1984; Shine et al, 2014) are consistent with both the reduced input of cholinergic neurons to the parietal cortices (Kuhl et al, 1996; Shinotoh et al, 1999; Perry et al, 1993) and a local loss of grey matter (Burton et al, 2004); whereas ventral dysfunction is highlighted by poor visuo-spatial memory and object recognition, and possibly by a greater LRP burden in the temporal cortex (Harding et al, 2002).

1.6 Psychosis

Psychosis refers to the distortion of an individual's perception of the world and/or their thought system, in PDD this most commonly presents as complex VH (e.g. seeing people or

animals; roughly 65% of cases; Fenelon et al, 2000; Henderson & Mellers, 2000; Aarsland et al, 1999; Aarsland et al, 2007) or delusions (e.g. the belief of an imposter within the patients dwelling; roughly 30% of cases; Marsh et al, 2004; Aarsland et al, 1999; Aarsland et al, 2007). The presence of psychosis is a significant factor for increased distress (Weintraub & Hurtig, 2007; Ricci et al, 2009), eventual nursing home placement (Goetz et al, 1995; Aarsland et al, 2000), and is a strong predictor of cognitive decline/dementia (Aarsland et al, 2007; Santangelo et al, 2007).

The risk of psychosis is increased with older age (Aarsland et al, 1999; Pacchetti et al, 2005; Sanchez-Ramos et al, 1996), longer disease duration (Fenelon et al, 2000; Pacchetti et al, 2005), as well as the use of dopaminergic medication (Henson et al, 2000), declining cognition (Fenelon et al, 2000; Pacchetti et al, 2005; Aarsland et al, 2001), and visual complaints (Diederich et al, 1997). The mixture of different risk factors makes it difficult to outline the pathophysiology of psychosis. However, emerging evidence from studies of medication and neurochemistry suggest that there may be a mixture of dopaminergic (Weintraub et al, 2006; Wolters, 1999), cholinergic (McKeith et al, 2000; Kuhl et al, 1996), and serotonergic (Melamed et al, 1996) contributions. Because psychosis tends to persist after the first episode (de Maindreville et al, 2005; Goetz et al, 2001; Ravina et al, 2007) there is increased pressure for efficient management of symptoms and precision diagnosis, in particular the latter of these is important for the safe prescription of appropriate medication due to the adverse reaction of LBD patients to typical antipsychotic medication (McKeith et al, 2005; Weintraub & Hurtig, 2007; Henderson & Mellers, 2000). To this extent there has been some success in the use of cholinesterase inhibitors (McKeith et al, 2000; Burn et al, 2006), and clozapine (French Clozapine Parkinson Study Group, 1999; Friedman et al, 1999; Pollak et al, 2004). However, in both cases the outcome of controlled treatment trials has demonstrated that whilst there is some cognitive improvement associated with these medications both are heavily dose dependent. The general disadvantage of this is the ceiling effect for improvement in both drugs. Whereas cholinesterase inhibitors improved cognitive functions higher doses also increased the presence of tremor (despite no general motor complications, Giladi et al, 2003), and were associated with greater likelihood of nausea (McKeith et al, 2000). Further, greater doses of clozapine resulted in increased sedation, and were also associated with anticholinergic effects and hypersalivation. Idiosyncratic agranulocytosis with clozapine is also a major concern requiring regular white blood cell counts to be taken thus overall reducing the efficacy of this as an independent treatment (Greene et al, 1993; Rudolf et al, 1997; Fernandez et al, 2003).

1.7 Diagnosis of PDD

A diagnosis of PDD is made if the patient presents with a UK brain bank diagnosis of PD paired with the presence of progressive cognitive decline across multiple systems that is severe enough to interfere with the running of everyday life (Emre et al, 2007). To aid the diagnosis the clinician is given a set of accompanying clinical, cognitive, and behavioural features (see **Table 1.1**), which might also be used to guide the diagnosis towards probable or possible PDD if the presence of the dementia syndrome is less clear. As a further point of clarity a distinction is made between a diagnosis of PDD and DLB based on the timing of the presentation of Parkinsonism relative to the onset of clinical and cognitive features (McKeith et al, 2005; McKeith et al, 1996; Emre et al, 2007): if Parkinsonism occurred in the year prior to the onset of cognitive symptoms a diagnosis of PDD is pursued, whereas a diagnosis of DLB is pursued if Parkinsonism began after the onset of cognitive symptoms.

Table 1.1 Diagnostic criteria for probable and possible PDD as described in the report from the Movement Disorders Study Task Force (Emre et al, 2007).

Features
<p><i>Core</i></p> <ul style="list-style-type: none"> • UK Brain Bank PD diagnosis • Presence of dementia syndrome: <i>Progressive cognitive decline.</i> <i>Impairment across multiple domains.</i> <i>Affects ability to conduct every day tasks.</i> <p><i>Accompanying features</i></p> <p><i>Clinical/Cognitive</i></p> <ul style="list-style-type: none"> • Impaired executive functioning. • Fluctuating, or otherwise impaired, attention. • Difficulties with language comprehension. • Visuo-spatial impairments. • Significant memory impairment <p><i>Behavioural</i></p> <ul style="list-style-type: none"> • Apathy • Personality/mood changes • Hallucinations • Delusions • Excessive daytime somnolence
Diagnosis
<p><i>Probable</i></p> <ul style="list-style-type: none"> • Both core features. • Typical pattern of cognitive impairment (at least two clinical/cognitive features), and at least one accompanying behavioural feature. • No comorbid factors (other influencing diseases or drug toxicity), or confusion over when the cognitive decline began. <p><i>Possible</i></p> <ul style="list-style-type: none"> • Both core features. • A-typical pattern of cognitive impairment (one clinical/cognitive feature). • Presence of behavioural features is not required.

The use of the one year rule to separate the diagnoses of PDD and DLB has been debated since its inception; on one hand there are arguments that the similarities in clinical presentation and gross pathology imply that DLB and PDD simply represent two different points along a spectrum of disease (Lippa et al, 2007; McKeith, 2007). For example, Aarsland and colleagues (Aarsland et al, 2004; Aarsland et al, 2001) reviewed literature covering the patterns of cortical atrophy and cellular pathology, as well as the neurochemical, and neuropsychiatric profiles in DLB and PDD. The authors demonstrated that in both cases it was widely reported that the cortex remained structurally intact, save for medial temporal lobe atrophy (Aarsland et al, 2004; Gomez-Isla et al, 1999; Broe et al, 2001; Shepherd et al, 2002), and that psychiatric symptoms (delusions and VH) although at increased frequencies in DLB presented similarly in both conditions (Aarsland et al, 2001). The counter argument to this viewpoint has focussed upon the differences in the development and distribution of cortical Lewy body pathology. For example, patients with DLB typically demonstrate a greater abundance of Lewy bodies within the temporal cortex than patients with PDD (Harding et al, 2002), which was proposed as an explanation for the increased proportion of VH in DLB patients relative to PDD patients. Further, in patients with PDD there are more pronounced deficits of the nigrostriatal system (Ouchi et al, 1999), which would account for differences in the extent of movement related extrapyramidal features in PDD and DLB (PDD 88% of cases, DLB 69% of cases, Burn et al, 2003). However, this argument falls short of describing different disease mechanisms. To this end it was posited that the two diagnoses could be contrasted based on the pathology predicting dementia severity; whereas dementia in PD was worsened by increasing frontal cortex LRP burden (Samuel et al, 1996; Kovari et al, 2003), the severity of the dementia syndrome in DLB was primarily believed to be related to the level of amyloid beta plaques in the neo-cortex (Harding et al, 2002; Mastaglia et al, 2003).

Despite there being some differences in the extent of the cognitive deficits experienced in PDD and DLB (Mosimann et al, 2004; Perriol et al, 2005), and some variations in the spatio-temporal pattern in the development of pathology (Lippa et al, 2007; Duda et al, 2002; Goldman et al, 2014), the overlap in terms of symptoms expressed and their presentation is remarkable. It could thus be seen that the one year rule is an entirely arbitrary marker to help divide two points on a spectrum based on the presentation of extra-pyramidal motor features (McKeith, 2007; Emre et al, 2007; Ballard et al, 2006).

1.8 Visual Hallucinations in Parkinson's disease with Dementia

Visual hallucinations (VH) occur in up to 65% of PDD cases (Aarsland et al, 1999; McKeith et al, 2005), and are linked to a complex pattern of cognitive decline and behavioural problems (Fenelon et al, 2000). The experience and phenomenology of VH are generally assessed using structured or semi-structured interviews (Mosimann et al, 2008) directed at either the carer (e.g. Neuropsychiatric Inventory Hallucinations subscale, NPI; Cummings, 1994), or the patient (e.g. the North East Visual Hallucinations Interview, NEVHI, Mosimann et al, 2008; Tottori University Hallucinations Rating Scale, TUHARS, Wada-Isoe et al, 2008). In the case of the NEVHI and the TUHARS both are also available as carer measurements, yet of all three measures only the NEVHI collects detailed information on the phenomenology of the VH (Urwyler et al, 2015; Urwyler et al, 2014). There are two major problems with this form of measurement, the primary issue is that as cognitive impairment worsens this increases the risk of the patient not being able to recall the hallucination accurately (or at all) due to memory failures (Levy et al, 2002; Bloomfield et al, 2016). The second problem is to do with communication between the patient and their carer. As well as instances of VH being unreported to the carer due to memory failure, the patient may feel a sense of social stigma surrounding the experience of VH, thus choosing to withhold information about their experiences in the hope of refraining from being labelled “insane” or not being taken seriously (Mosimann et al, 2008; Urwyler et al, 2015). An attempt to combat this has been made in the design of the NEVHI, which makes a conscious effort to guide the patient into talking about imagery and false perceptions, whilst not outright labelling these as VH in the first instance (Mosimann et al, 2008). The implication of this is improved reliability and validity in the reporting of phenomenology as well as providing temporal information, thus helping to provide better qualitative information which might be of further use in the study of aetiology.

The typical phenomenology associated with complex VH in PDD will consist of one or a combination of the following: people/faces (84% of cases), animals/insects (37% of cases), and/or objects (39% of cases; Ferman, 2007; Cagnin et al, 2013; Erskine et al, 2015; Mosimann et al, 2006; Urwyler et al, 2014). However, less complicated percepts such as patterns and geometric shapes, or disjointed morphologies might occur in lieu of complex VH, especially at the earlier stages of PD (Pagonabarraga et al, 2014; Llebaria et al, 2010; this is discussed in greater detail below). As the disease progresses the VH experienced will often become more exaggerated (Williams-Gray et al, 2007; McKeith & Burn, 2000), and are often accompanied by a loss of insight (Cagnin et al, 2013; Barnes et al, 2003). Whilst this

progression can manifest as a totally harmless, or even as an enjoyable experience (e.g. attempting to converse with hallucinations of relatives or friends), the combination of complex or more frightening imagery with poor meta-cognition regarding the nature of the percept (e.g. Varese & Bentall, 2011) can increase anxiety for both the patient and caregiver (Ricci et al, 2009; Factor et al, 2003). The consequence of this is increased likelihood of nursing home placement and reduced quality of life (Goetz & Stebbins, 1993; Goetz & Stebbins, 1995). This leads into the central concern which is that of how best to treat/manage the symptom with a view to improving quality of life (Boström et al, 2007; Levy et al, 2002). However developing effective therapies for VH remains a challenge due to a poor understanding of VH aetiology in PDD.

1.9 Understanding the Mechanisms of VH in PDD

1.9.1 The Distinction between Bottom-Up and Top-Down Processing

In its most simple form the visual system can be divided into bottom-up and top-down processes, and this distinction helps with characterising the direction of information processing/communication, and what role the processing plays in the overall task of perception. Bottom-up refers to the processes involved in feeding information into the system (retina and pre-striate pathways) and breaking it down into its individual elements (cortical processing in the striate and extra-striate cortices), whereas top-down refers to the application of attentional control based on context or task demands to guide the processing of the information contained within the visual scene (e.g. frontal cortices and the neuronal populations connecting them and other cortices, Onofrij et al, 2013). Although this is an oversimplification of the processes involved in visual perception it serves the purpose of helping construct models of VH.

1.9.2 Development of the Scientific Perspective on VH in PDD

Early approaches to the general study of VH believed that problems with the eye were the primary cause of VH (Morax, 1922; see ffytche, 2007 for a detailed historical account of VH models), suggesting that illusory percepts arose as a form of positive scotoma caused by optic nerve damage or loss of retinal cells (Morax, 1922). This opinion gathered support over many decades based on the observations of those with Charles Bonnet syndrome, in which VH present in the absence of cognitive impairment. Whilst this opinion would help to lay the foundations for modern deafferentation theories (Burke, 2002; Cohen et al, 2000; Cogan, 1973), it failed to account for both the percept phenomenology and the observation that “not all with eye disease hallucinate, and not all who hallucinate have eye disease” (Terson, 1930;

ffytche, 2007). It has come to be appreciated that the experience of complex visual phenomena in the absence of (or only very mild) visual impairment would be very unlikely without some level of cognitive impairment preventing the disambiguation of visual information (Urwyler et al, 2014; Shine et al, 2011). Furthermore, in most cases of schizophrenia (Waters et al, 2012; Mueser et al, 1990), and in a reasonable number of cases involving Lewy bodies the patient will experience either concurrent or isolated hallucinations in other modalities such as auditory or haptic (Onofrj et al, 2013; Fenelon et al, 2002; Tousi et al, 2004). It should therefore be argued that hallucinations are equally likely to involve dysfunctional communication and disturbed perception. However, it is only more recently that there has been a transition towards a school of thought concerning holistic, or integrative models of VH (Onofrj et al, 2013; Collerton et al, 2005; Diederich et al, 2004; Shine et al, 2011). With this in mind there is still much work to be done in terms of classifying the balance of contributions from different levels of processing (i.e. top-down vs. bottom-up) which are likely to vary across different VH-prone diseases.

The integrative approach to understanding VH in PDD states that VH arise as a result of dysfunctions within discrete elements of the visual system (such as the retina, dorsal stream, ventral stream, and primary visual cortex) as well as the executive systems that control communication within and between these elements (e.g. Collerton et al, 2005; Diederich et al, 2004; Shine et al, 2011). This approach has grown in strength in recent years due to its inclusion of structural and metabolic changes in different regions of the visual system in PDD patients with VH (*occipital hypometabolism*, Colloby et al, 2002; Gasca-Salas et al, 2015; *frontal and visual association grey matter reduction*, Burton et al, 2004; Ramirez-Ruiz et al, 2008; Yao et al, 2016; Pagonabarraga et al, 2014; Goldman et al, 2014; *elevated temporal cortex Lewy body density*, Harding et al, 2002) which support earlier cortical models of aberrant regional activity (e.g. ffytche et al, 1998); whilst also acknowledging that the output of the perceptual process is the result of communication along dynamic feedback loops that allow for the supervised rendering of a visual percept (Bullier, 2001). It was described above that VH in PDD are associated with greater cognitive impairment (Fenelon et al, 2000; Pachetti et al, 2005; Aarsland et al, 2001) and disturbed visuo-spatial attention (e.g. Hu et al, 2014; Mosimann et al, 2004) therefore meaning that it is appropriate to consider that top-down control of visual processing and perception (including the binding of visual information to semantic objects) is disturbed in PDD. An example of this is the interaction between the environment and visuo-perceptual errors made by those who hallucinate compared with those who don't. When visual conditions are of poor quality, such as low levels of lighting (Goetz

et al, 2006; Barnes & David, 2001), the recognition of objects is impaired in PDD patients with VH (Meppelink et al, 2008; Meppelink et al, 2009; Fenske et al, 2006; Grill-Spector et al, 2000). Similarly, when asked to respond to congruent and incongruent visual cues, representing which arrow key to press, the number of correct responses was reduced when more competing/distracting stimuli were present (Hall et al, 2016). The role of top-down control of attention is also supported by a number of neurochemical/neuropathological findings (described in greater detail below), which associate the presence of VH with a reduction in choline acetyltransferase (Perry et al, 1990; Perry et al, 1995; McKeith et al, 2004), and the denervation of corticopetal cholinergic neurons from the nucleus basalis of Meynert (NBM; Gratwicke et al, 2013; Bohnen et al, 2011). The physiological correlate of this is believed to be a reduction in the ability to regulate the modulation of synaptic gain (or cortical excitability) in response to different visual stimuli as demonstrated in the power of the electroencephalography (EEG) posterior alpha rhythm (e.g. Chaumon et al, 2014; Rajagovindan et al, 2010; Händel et al, 2011; Romei et al, 2008; Romei et al, 2010). Direct evidence of attentional impairments in the framework of VH is provided by the noticeable reduction in VH frequency, and increase in posterior EEG alpha power, following the administration of cholinesterase inhibitors such as rivastigmine (McKeith et al, 2004; McKeith et al, 2000; Burn et al, 2006; Bosboom et al, 2009).

In essence the integrative approach considers that VH generation is the result of a failure in the predictive coding (e.g. Pajani et al, 2015; Meppelink et al, 2009) of visual information due to disturbances in bottom-up and top-down processing of information, thus failing to correctly interpret certain elements of the visual scene. This is best described in the perception attention deficit model (PAD, Collerton et al, 2005). Here a series of proto-objects for individual items are generated based on expectations/context and the best fit is matched with the input visual information to bring the item to conscious awareness. Visual hallucinations are theorised to occur when the visual input is degraded and poorly processed, impeding the executive process of matching the signal to the correct impression of the image, thus mistaking the input for something else.

The increasing popularity of the use of functional connectivity analysis to study the integrity of cognitive networks using functional magnetic resonance imaging (fMRI) has helped with providing several strong lines of empirical evidence to support the overall integrative approach to VH. Multiple studies have described changes in the integrity, and activity, of the dorsal (DAN) and ventral attention networks (VAN), as well as the default mode network (DMN; e.g. Shine et al, 2012; Shine et al, 2014; Perazza et al, 2014; Yao et al, 2016).

Although these networks serve different purposes (DAN, *direction and maintenance of goal/context driven attention*; VAN, *stimulus driven attention*; DMN, *task-independent, internal thought, “mind wandering”*), they work in a complimentary fashion in order to process and integrate visual information with the correct semantic information. Shine and colleagues posit that, following initial impairments in visual input, VH arise due to poor conflict resolution when attempting to disambiguate the visual image (Shine et al, 2011). Dysfunction of the DAN as a result of Lewy body pathology impairs the ability to interpret the image based on contextual and apriori information, resulting in an over reliance upon the VAN and the DMN (Shine et al, 2011). Neither the VAN nor the DMN are functionally equipped to accurately interpret the image and thus salient features from autobiographical information are attributed to the signal (Shine et al, 2011; Hall et al, 2016; Yao et al, 2014). The disruptions highlighted in such network analyses are consistent with the pattern of changes highlighted in previous structural and metabolic studies (e.g. Burton et al, 2004; Colloby et al, 2002; Harding et al, 2002; Rektorova et al, 2014; Yao et al, 2016), and with the pattern of executive impairment (Emre et al, 2007; Aarsland, 2016). Combined with the likelihood of alterations to the neural circuitry in the primary visual cortex (e.g. Pajani et al, 2015) there is strong evidence in favour of VH in PDD being the product of dysfunctional network behaviour, and not simply a case of isolated aberrant activity.

Although there is strong evidence supporting a mixture of perceptual and attention impairments leading to the genesis of VH it is important not to stray from the aforementioned statement by Terson (Terson, 1930), that “not all with eye disease hallucinate and not all who hallucinate have eye disease.” In this case the statement translates to the pattern of cognitive and perceptual impairments in PDD, as in most cases there is a degree of visual impairment but not all cases with visual impairment will hallucinate (e.g. Goldman et al, 2014). Likewise, not all who have some level of cognitive impairment are guaranteed to report VH. Simple VH have previously been used as an intermediate for studying this relationship (e.g. Urwyler et al, 2014; Pagonabarraga et al, 2014), as they represent an umbrella of different visual percepts (e.g. geometric patterns & shapes) and sensations (e.g. feelings of presence or movement), but do not manifest as complex phenomenology that appear to interact with the world around the individual. A recent exploration of the neuropsychological correlates of VH in PD drew a distinction between the patterns of cognitive impairment in those with simple vs those with complex VH, finding that simple VH began during a stage of little to no cognitive impairment, and that the severity of VH was increased linearly with cognitive impairment (Llebaria et al, 2010). This fits alongside imaging findings which noted only a pattern of

dorsal stream structural deficits in PD with simple VH compared to controls (Pagonabarraga et al, 2014). A similar distinction has been drawn between simple and complex VH in PD patients (controlling for cognitive impairment), testing the predictive power of visual complaints such as blurred vision, double vision, and dry eyes, for the presence of simple and complex VH (Urwyler et al, 2014). The authors found that visual complaints predicted passage and presence (simple VH) hallucinations, but were unrelated to the occurrence of complex VH (Urwyler et al, 2014). These findings demonstrate that simple and complex VH both share a common ground in terms of the disturbance of early visual processing, but that complex VH are dependent upon the further development of cognitive complaints. Finally, the Urwyler findings demonstrate the importance of disturbed visual input for the generation of certain simple visual hallucinatory phenomena (Urwyler et al, 2014). This underlines that it is still unclear what the size of the contributions from each of the different components implicated in VH generation are.

Therefore, whilst it is understood that particular structures are impaired, and that this has consequences for the overall task of visual processing, it remains unclear how this impaired ability to communicate manifests. Using structural and functional neuroimaging is limiting for understanding how synaptic activity is altered and therefore it is necessary to consider the enhanced temporal resolution afforded by electrophysiological methods for exploring of the aetiology of VH generation in PDD.

1.10 Using Electrophysiology for Understanding the Dynamic Flow of Visual Cortical Activity

1.10.1 Electroencephalography in PDD

Electroencephalography (EEG) uses small metallic electrodes placed on the scalp to measure the spontaneous or event related changes in synaptic potential generated by clusters of pyramidal neurons within the cerebral cortex. This provides a time-sensitive measurement of synaptic communication which can be studied using a variety of approaches, the most common of which is the event related potential (ERP). The ERP is a signal containing a number of peaks and troughs (components) representing the regional summation of action potentials at a given latency relative to an event (e.g. the presentation of a stimulus, or the pressing of a button). The measurement of component amplitudes and latencies is used to gauge how a given population of neurons respond to a particular event and how their activation is modulated by different conditions. Further, these measurements can be used to draw inferences about the efficiency of cortical processing in clinical populations versus

controls. It is also possible to estimate the frequencies of neuronal activity in either resting or active states, which represents the synchronous activation of clusters of neurons during local (typically high frequency) or inter-regional (typically low frequency) communication. Although these methods provide a time-sensitive measurement of synaptic communication the caveat of recording potentials from the scalp is the distortion of the spatial information. The information recorded at any given point on the scalp represents a mixture of activity from different sources, however, due to the effects of volume conduction (Nunez & Srinivasan, 2006) we are presented with the “inverse problem”. Thus, without information about the medium travelled through, and precise shape of the head it is difficult to make any inferences regarding the precise generator of a scalp potential. Although algorithms for source estimation are improving there is still no perfect way to pinpoint the structural architecture of the EEG signal.

1.10.2 Event Related Potentials

Although it is difficult to infer the precise generators of the ERP response the study of temporal patterns has the advantage of being able to observe whether patterns of communication related to a particular process, or task, are inherently dysfunctional or whether communication is only altered at specific points in time. For the study of VH this is particularly powerful as it provides a greater mechanistic insight that can then be considered in the context of known structural and functional abnormalities. Across the spectrum of Lewy body diseases there are a wealth of reports associating cognitive impairments with changes in the amplitude and latency of several ERP components. In particular, changes to the amplitudes and latencies of the P3, N2, contingent negative variation (CNV), and processing negativity (PN) components have been reported. These components each reflect processes for the management of resources dedicated to perceptual processing in the auditory and visual domains (depending upon the modality of the stimulus). Each component has demonstrated some level of improvement following the administration of dopamine agonists such as levodopa (Starkstein et al, 1989; Oishi et al, 1995; Amabile et al, 1986), suggesting that the broad cognitive architecture of attentional control is at least partly affected by the depletion of dopaminergic neurons ascending from the substantia nigra in PDD (Treitakoff, 1919; Ma et al, 1997; Rinne et al, 1989). Furthermore the manipulation of these components relative to healthy controls shows that whilst the functions of stimulus discrimination (P3), inhibitory control, and response preparation in adherence to contextual rules (N2, CNV, PN) are impaired they are not completely lost. For example, when presented with images of their own face (target) and other random (sex and age matched) faces (non-target), the P3 response to

the target stimuli was significantly delayed in LBD patients compared with controls, but task performance was still possible (Kurita et al, 2010). This mix of findings relating to general and visual attention are important for the study of VH as they help to demonstrate that there is poor communication between the perceptual and executive cortical regions (which as noted above has been implicated in VH generation). Further, this aids with discriminating when the communication is disrupted, relative to the input of visual information. This point represents a strength of EEG (in particular ERPs), in that it becomes possible to discern whether processing is likely to be inherently dysfunctional, or if a particular system is affected by a combination of different conditions.

1.10.3 Visual Input

Early electrophysiological studies of perception in PD and PDD used the presentation of different dynamic visual stimuli, such as patterns and flashing lights, to investigate the integrity of visual input (e.g. Nightingale, et al, 1986; Bodis-Wolner et al, 1978). Much like various cognitive paradigms these methods also produce an ERP which can be recorded directly from the retina (electroretinography, ERG) or from the primary visual cortex (visual evoked potential, VEP). Both the ERG and VEP have been widely studied in PD, and whilst there exists some contention between findings (Tagliati et al, 1996; Erskine et al, 2015), there is enough evidence to suggest that LRP is associated with some level of deficient function within the retina (Nightingale et al, 1986; Onofrj et al, 2006; Diederich et al, 1998; Pieri et al, 2000; Archibald et al, 2009; Nowacka et al, 2015) and the transfer of the visual signal to the primary visual cortex (Matsui et al, 2005; Okuda et al, 1995; Bodis-Wolner et al, 1978; Bodis-Wolner & Antal, 2005; Bandini et al, 2001).

In both the ERG and the VEP the waveform components are typically shown to have reduced amplitudes when compared with those of the control group, which is believed to stem from the depletion of dopaminergic cells in the retina exerting a negative influence upon the activity of photoreceptors at multiple retinal layers (Archibald et al, 2009; Maurage et al, 2003; Nowacka et al, 2015; Shulman & Fox, 1996; Krizaj et al, 1998). The consequences of this for perception are poor visual acuity, difficulties with the control of image contrast, and reduced sensitivity to colour and motion (Archibald et al, 2009). Urwyler et al, described a positive relationship between the presence of visual complaints and the experience of simple VH in PD (Urwyler et al, 2014), which might partly be explained by the pathophysiology of PD at the level of the retina. For example the depletion of retinal dopamine leads to poor control of surround inhibition, and as a result the flexible control of contrast for efficient separation of image features is affected (Dowling et al, 1986; Archibald et al, 2009; Nowacka

et al, 2015). The degraded image sent to the visual cortex could thus manifest as a feeling of presence, or a simple misperception (Diederich et al, 2004; Onofrj et al, 2006). The improvement of these measurements in response to levodopa treatment (Starkstein et al, 1989; Oishi et al, 1995; Amabile et al, 1986) supports that there is some role of the pre-striate dopaminergic system in the VH experienced in PDD. However, it is necessary to contrast this against the observation that dopaminergic medications can exacerbate the experience of VH, suggesting that the distribution and impact of dopamine depletion within the visual system as a whole is a complex issue.

As well as the control of cellular communication within the retina the structural integrity of the pre-striate pathways between the retina and the primary visual cortex is considered to exert some influence over the generation of VH. Studies using the pattern reversal VEP have previously made inferences about this based on the latency of the P1 (or P100) component, finding that it is elongated in patients with PD and it has been suggested that the conduction of the signal is slowed by some factor related to PD pathology (Matsui et al, 2005; Bodis-Wolner et al, 1978). In PD patients, Matsui et al, found that increasing latency of the P1 was a strong predictor for the experience of VH, suggesting that inefficiencies in the transmission of information from the eye associates with the development of VH (Matsui et al, 2005). Source localisation of the VEP P1 component in healthy controls shows that its origins are in V2 and the extra-striate cortices (Di Russo et al, 2002; Di Russo et al, 2005), meaning that the P1 is representative of higher level visual processing. Instead of the P1 it would be more appropriate to consider the N1 (or N75) component of the VEP as a marker of conduction velocity due to it being generated by thalamo-cortical projections between the lateral geniculate nucleus (LGN) and V1 (Di Russo et al, 2005). However there is a paucity of research surrounding the involvement of the N1 component in LBD research, and also in VH research. Nevertheless, under the traditional interpretation of P1 latency the extended latency of the P1 component has previously been demonstrated as a predictor of VH in patients with PD (Matsui et al, 2005), supporting the involvement of visual input/early bottom-up visual processing in the experience of VH. Other investigative approaches have sought to determine if there are any effects of LRP on the lateral geniculate nucleus (LGN) and found that compared with controls, in the LGN pathology is still only relatively low in LBD patients; further both groups had shown similar levels of BOLD activation during fMRI prior to death (Erskine et al, 2015). Interestingly, although the LGN is relatively spared in LBD thinning of the optic nerve fibre layer has been related to the experience of VH in PD without dementia (Lee et al, 2014). It is beyond the scope of this text to comment on how this might influence

the transmission delay of the visual signal, however, the combination of poor quality retinal output and an intact LGN might be a pre-requisite state for the development of VH (Erskine et al, 2015). In this case whilst the LGN transfers information to the cortex effectively, pregeniculate input remains compromised. Also whilst this provides some basis for bottom-up contributions to VH generation in LBD, it falls short of describing a complete mechanism.

1.10.4 Top-Down Control

In order to efficiently manage the processing of visual information top-down modulation of the visual cortex neurons is applied to selectively control the rate of firing in response to different visuo-spatial information (Händel et al, 2011; Chaumon et al, 2014; Rajagovindan et al, 2010). In EEG the control of attention related to visual perception is measured in terms of the power and phase of the posterior alpha rhythm (8-14Hz; Romei et al, 2008; Romei et al, 2010; Mathewson et al, 2009), which is believed to represent cholinergic communication between the frontal and occipito-parietal cortices mediated by the thalamus (Capotosto et al, 2009; Capotosto et al, 2012; Bosboom et al, 2009; Goldman et al, 2002; Larson et al, 1998; Lingdren et al, 1999; Schreckenberger et al, 2004). A simple example of this is the lateralisation of occipital alpha power during the orienting of visual attention, in which case the alpha power is reduced over the hemisphere contralateral to the position of the attended to item representing increased cortical excitability through reduced inhibition (Handel et al, 2010; Thut, 2006; Worden, 2000). However, alpha rhythm activity as a form of inhibitory control is not just a case of suppressing processing in one region to improve processing in another; for visual perception alpha power and its phase demonstrate a dynamic relationship with the cortical response to a stimulus (e.g. Chaumon et al, 2014; Mathewson et al, 2009; Jensen et al, 2012; Britz et al, 2014). For example, visual detection performance on stimuli with varying contrast disparities is improved with lower posterior cortical alpha power (Chaumon et al, 2014). Further, target detection can be predicted by reduced alpha power, and the N1 component amplitude associated with presentation of the visual stimulus is increased when the phase of the pre-stimulus alpha rhythm is reversed relative to non-detected trials (Mathewson et al, 2009). Therefore the alpha rhythm represents not simply a form of inhibition but a mechanism by which to regulate the sensory gain of pyramidal neuron clusters to control the efficiency of perception (Lange et al, 2014; Chaumon et al, 2014; Rajagovindan et al, 2010; Handel et al, 2010; Bazanova, 2012).

Patients with PDD will often exhibit altered patterns of the alpha rhythm such as a slowing of the peak alpha frequency towards a high-theta rhythm (Bonanni et al, 2008; Bonanni et al, 2015; Stoffers et al, 2007; Bosboom et al, 2006), and a global reduction in the

amplitude/power of the alpha rhythm (Bosboom et al, 2006; Bosboom et al, 2009; Babiloni et al, 2011; Soikkeli et al, 1991) - which has further been demonstrated as a marker of cognitive decline (Bonanni et al, 2015). The alpha rhythm measurements in PDD are subsequently improved in response to rivastigmine (Bosboom et al, 2009), whilst the experience of VH is also alleviated following cholinergic treatment (Burn et al, 2006). This supports earlier studies of pathology in which depleted choline acetyltransferase was correlated with the presence of VH (Perry et al, 1993; Perry et al, 1995), but has so far not seen conclusions regarding the role of the alpha rhythm in the genesis of VH in PDD.

It is possible that the impairment of the alpha rhythm in PDD leads to a reduction in the ability to efficiently modulate visual attention, leading to excess visual information flooding the system. As a consequence the control of neuronal gain is less selective and therefore increases the amount of irrelevant visual information which might bias or confuse the interpretation of information during active processing (Lange et al, 2014; Linkenkaer-Hansen et al, 2004; Zhang & Ding, 2010; Yokoi et al, 2014). Conversely, this might reflect a compensatory process to increase the chances of correctly matching some visual information, based on the poor quality of visual input and perceptual processing (e.g. Bodis-Wolner & Yahr, 1978; Nightingale et al, 1986; Lee et al, 2014; Yao et al, 2016; Burton et al, 2004; Mosimann et al, 2004), with the cost being an increased susceptibility to VH. Although the evidence available suggests some level of cholinergic involvement in the generation of VH there have been no direct investigations of the role played by the alpha rhythm (as a physiological correlate of cholinergic activity) in the genesis of VH. Therefore it may be more a representation of global cognitive decline (Bonanni et al, 2015) rather than being a specific causal factor for VH in PDD.

1.10.5 Transcranial Magnetic Current Stimulation

As well as recording the dynamic flow of visual information processing it is possible to directly manipulate the signalling of cortical pyramidal neurons and observe the behavioural, and even physiological (e.g. BOLD response, Bohning et al, 2000; event related potential, Taylor et al, 2010; spectral response, Herring et al, 2015), responses between groups or conditions. Although this is possible via many different methods (for reviews of these approaches please refer to Pascual-Leone & Walsh, 2003; & Murphy et al, 2015), transcranial magnetic current stimulation (TMS) is perhaps the most widely used method – most likely due to its focality, non-invasiveness and tolerability compared with earlier electrical stimulation methods. The passing of an electrical current through a metallic winding within the coil body generates a magnetic field, which when passed through the scalp generates an

electrical field (Barker et al, 1985). The electrical field depolarises the axons of the pyramidal neurons aligned perpendicular to the cortical surface generating an action potential. However, due to the rapid dissipation of the magnetic field strength with increasing distance from the coil the stimulation of neurons is restricted to relatively superficial layers of the neo-cortex (Walsh & Pascual-Leone et al, 2003). There are a vast range of methodologies possible through the use of TMS such as studying the chronometry of behaviour (e.g. varying the timing of TMS relative to a visual stimulus onset to determine the time course of conscious awareness, Amassian et al, 1989), cortical excitability (e.g. the level of stimulation required to elicit a phenomenon, discussed in more detail below), or regional contributions to cognition (e.g. the interjection of “noise” to a region during a cognitive task). More recently TMS has also demonstrated utility for the induction of neuroplastic changes through long term application of repetitive trains of pulses (rTMS), which has lead others to believe it could have therapeutic uses (Merabet et al, 2003; Meppelink et al,2010).

Transcranial magnetic current stimulation has been widely used to study the visual system in healthy controls but has seen limited use in the PDD and DLB populations, and in particular sparse application for understanding VH. The research available which has investigated VH in LBD has primarily fixated upon understanding the crude physiology of top-down control at the level of the primary visual cortex helping to expand the train of thought for how pathological changes to cortical excitability might be involved in the genesis of VH in LBD (e.g. Taylor et al, 2011). In a comparative study of DLB patients and healthy controls TMS was used to elicit illusory visual percepts called phosphenes (Taylor et al, 2011). The authors measured the threshold (percentage output of the TMS generator required to elicit phosphenes) and phenomenological complexity of phosphenes in both groups and determined that at the broad level these measurements were similar between groups. The similarity in the generation of phosphenes suggested that the pathway(s) involved with their information processing (e.g. Caparelli et al, 2010) remain largely intact in the presence of LBD pathology (Taylor et al, 2011). This serves to further highlight that the visuo-perceptual problems leading to the argument that the experience of VH is predominantly grounded in the dynamics of communication rather than the physical centres for visual processing. However, an interesting extension of these findings was the negative relationship between NPI hallucinations subscale severity/frequency of VH (VH severity) and the phosphene threshold, such that cortical excitability appeared to be increased in patients with more severe hallucinations. The authors claimed that this could be due to the naturally high variability in phosphene thresholds between individuals, and that those in the DLB group may have been

predisposed to the experience of VH by their pre-morbid natural affinity for enhanced cortical excitability (Taylor et al, 2011). However, in the absence of any longitudinal evaluations of how such properties might be implicated in the development of LBD and subsequently VH it is difficult to make firm conclusions about the Taylor finding, yet this does provide solid foundations for future investigations in terms of the developmental aspects of VH aetiology.

1.10.6 Concurrent TMS & EEG

The electrophysiological literature reviewed above provides support for both top-down and bottom-up visual system dysfunction in PDD in line with the integrative approach to VH understanding (Collerton et al, 2005; Shine et al, 2011; Diederich et al, 2004). Further, these might provide utility as physiological markers in the study of VH mechanisms. However, there is still a knowledge gap concerning the pathophysiology of synaptic communication in the dorsal and ventral streams during active visual perception. Through the combination of TMS and EEG it is possible to measure the spatio-temporal response to stimulation, as well as how this interacts with behavioural and physiological correlates of cortical excitability (e.g. phosphenes, Taylor et al, 2010; Romei et al, 2008; Matthewson et al, 2009; Kommsi et al, 2004). Because TMS during consciousness activates a network of functionally connected sites (Garcia et al, 2011; Massimini et al, 2005) it is possible to study the spatio-temporal sequence of communication using the TMS evoked potential (TEP; e.g. Taylor et al, 2010; Bagattini et al, 2015), or to make inferences about the populations of neurons involved within the sequence using spectral coherence measurements (Garcia et al, 2011). Further, through investigation of pre-stimulation spontaneous activity it has been possible to draw inferences about the manner in which the brain switches between states to engage in visual perception (Romei et al, 2008; Romei et al, 2010; Matthewson et al, 2009).

These investigations in healthy controls have helped to pioneer an understanding of the physiology underlying active visual perception previously only speculated upon. With the enhanced spatio-temporal resolution available it should follow that this approach would be ideally suited to identifying markers of regional synaptic pathology in PDD, and how the patterns of communication described are modified in those who experience (or will go on to experience) VH.

In summary, dementia in Parkinson's disease is associated with a broad pattern of physiological changes which underpin the features of global cognitive decline and visuo-perceptual disturbances. Although our understanding of the symptoms and their management has improved, the effective treatment of VH remains a challenging task due to a fragmented

understanding of their aetiology. Electrophysiology is an important avenue for the continued research into the contributing features of VH and how they interact. This thesis expands upon previous electrophysiological studies of bottom-up and top-down processing in the PDD visual system in an attempt to understand how they are affected by Lewy body pathology and further how they are manipulated in the development of ever more severe VH.

Chapter 2 Aims, Objectives and Hypotheses

2.1 Aims

The primary aim was to investigate the electrophysiological correlates of synaptic communication within the visual system in Parkinson's disease with dementia (PDD), and to contrast these with measurements taken from healthy controls. The intention was that by assessing several different elements of visual processing it would be possible to understand the balance between apparent top-down and bottom-up processing/communication disruptions in the aetiology of visual hallucinations (VH).

2.2 Objectives and Hypotheses

2.2.1 Visual Evoked Potentials

The visual evoked potential (VEP) was used as a measure of bottom-up processing, covering contributions from pre-striate information transfer as well as the early processing of basic visual information at the primary visual cortex, which have both previously been inferred to be disrupted in PDD. However the role of these disruptions is currently debated in the VH literature.

Hypotheses

- VEP component amplitudes will be diminished in PDD compared to controls reflecting poorer retinal processing in the former.
- Pre-striate information transfer speed, as demarcated by the N1 component latency should be reduced in the PDD group, as a result of retinal and optic radiation structural changes associated with Lewy body pathology. Although this is typically demarcated by the latency of the P1 component, based on source localisation studies of the VEP components (see **Chapter 1**) it is argued that the N1 would represent a more anatomically accurate marker of pre-striate information transfer.
- Based on previous findings the VEP P1 component will demonstrate increased peak latency in the PDD group. If as suggested in **Chapter 1**, the content and/or severity of the VH are related to poor interpretation of visual input the reduced efficiency of early visual processing, as demarcated by the P1 component latency, should be positively correlated with the scores for the severity of VH in the PDD group.

2.2.2 Transcranial Magnetic Current Stimulation

Transcranial magnetic current stimulation (TMS) was used to study multiple aspects of visual processing. Measurement of the component amplitudes and latencies from the general response to TMS during concurrent EEG provides an insight into the feed-forward and feed-back processing evoked by the stimulation of primary visual cortex. Further the use of TMS to elicit phosphenes allows for the study of the response to increased perceptual and attentional demands

Hypotheses

- Based on the presumed relative structural integrity of the cortical visual system in PDD the general TEP measurements (no-phosphenes) will be relatively similar between PDD and control groups, but TEP will not respond as efficiently during phosphene perception due to the disruption of systems controlling higher perception and attention.

2.2.3 Power Spectral Density

The power spectral density for the alpha and pre-alpha bands was measured during resting and in the period prior to stimulation, as these have previously been used as correlates of the top-down control of visual attention and communication between the lower and higher visual systems. Previous studies of PDD and dementia with Lewy bodies (DLB) have shown that oscillatory activity within this range is altered possibly reflecting changes to neurochemical communication. These changes are currently not understood in the context of VH.

Hypotheses

- Alpha power in the PDD group will be characterised by a slowing of the peak alpha rhythm in alignment with previous studies.
- Both control and PDD groups will experience a reduction in peak alpha power during the pre-stimulus period of phosphene trials (from the concurrent TMS and EEG recording) relative to no-phosphene trials.
- Physiological correlates of poorer control of visual attention as measured by the posterior alpha rhythm will be associated with the reporting of more severe VH experiences in PDD patients.

Chapter 3 General Methods

“...but logic is not all; one needs one's heart to follow an idea.” –*The Relation of Science and Religion*,
R. Feynman (1956)

This chapter describes the methods that were used during the acquisition and analysis of electrophysiological data. The basis of this thesis and the studies described here are part of a larger, on-going, study into visual hallucinations (VH) in Parkinson's disease with dementia (PDD) (the VEEGStim study, see **Figure 3.1**).

3.1 Subjects and Recruitment

A total of $n = 43$ participants were recruited from three participant populations: *PDD with VH* ($n = 19$), *PDD without VH* ($n = 7$), and *healthy age matched controls* ($n = 17$). Patterns of attrition and exclusion are summarised in **Figure 3.2**. Ethical approval was granted by the Newcastle National Health Service (NHS) ethics committee covering the screening and recruitment of participants located under the following NHS foundation trusts: Newcastle upon Tyne Hospital (NUTH); Northumberland Tyne and Wear (NTW), Northumbria, Gateshead, Tees, Esk, and Wear Valley.

Participants were identified through contact with consultants in old age psychiatry, geriatrics, ophthalmology, neurology and memory services, and by case-note searching (performed by the staff of the North-East Local Research Network of the Dementias & Neurodegenerative Diseases Research Network; DeNDRoN). Diagnosis and group placement was overseen by an experienced clinician (Dr John-Paul Taylor). Suitable participants were contacted in writing to extend an invitation to participate in the study (see **Tables 3.1 & 3.2** for inclusion and exclusion criteria). Healthy control participants were identified from case registers and from previous research participant lists.

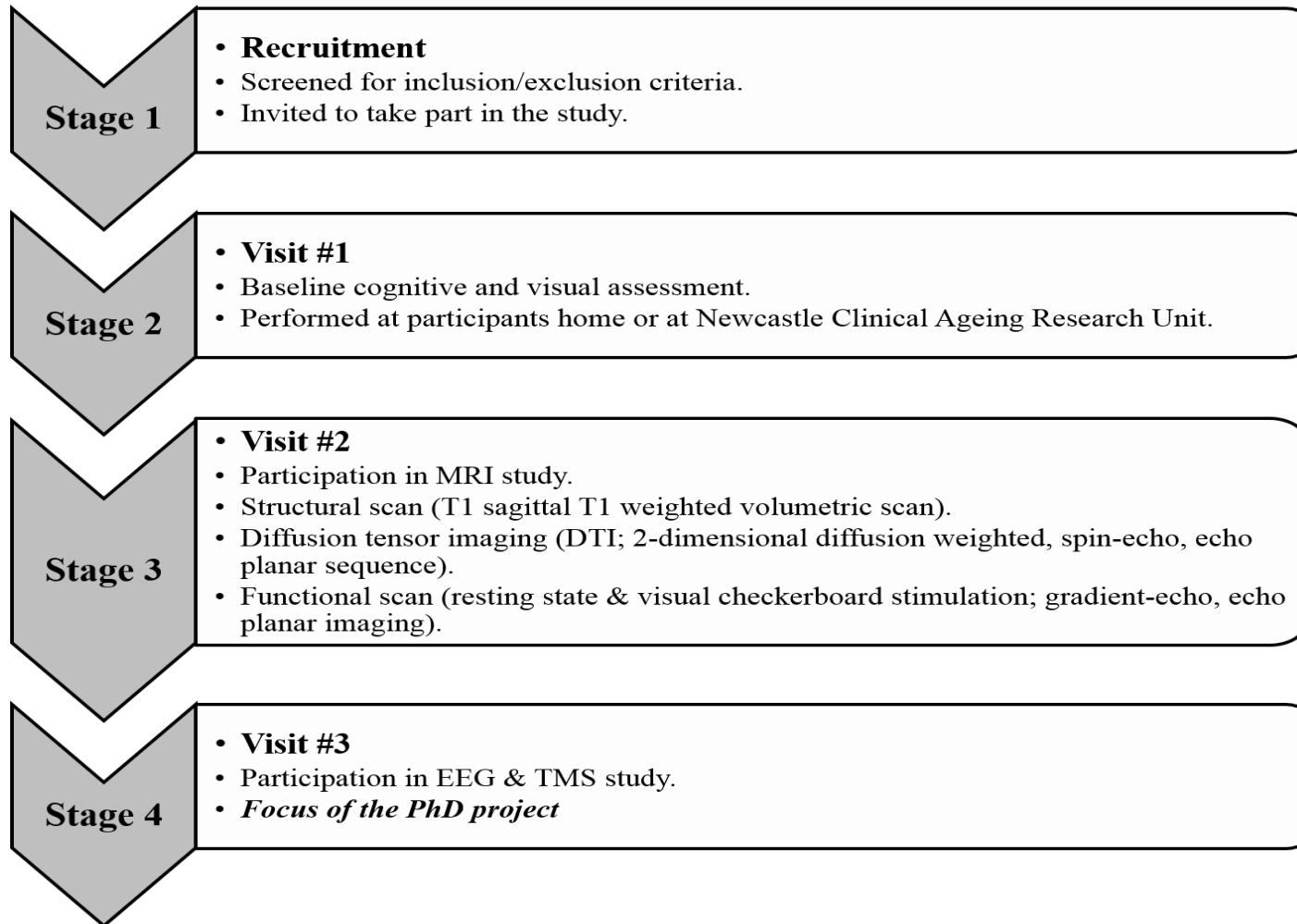


Figure 3.1 Design of the VEEGStim study (Visual Hallucinations: an EEG and non-Invasive Stimulation Study). The study described in this body of work utilises elements of the data collected at stages 2 and 4, whilst the structural magnetic resonance images (MRIs) from stage 3 were used to aid the neuronavigation of the transcranial magnetic current stimulation (TMS) coil.

Recruitment Numbers and Group Attrition

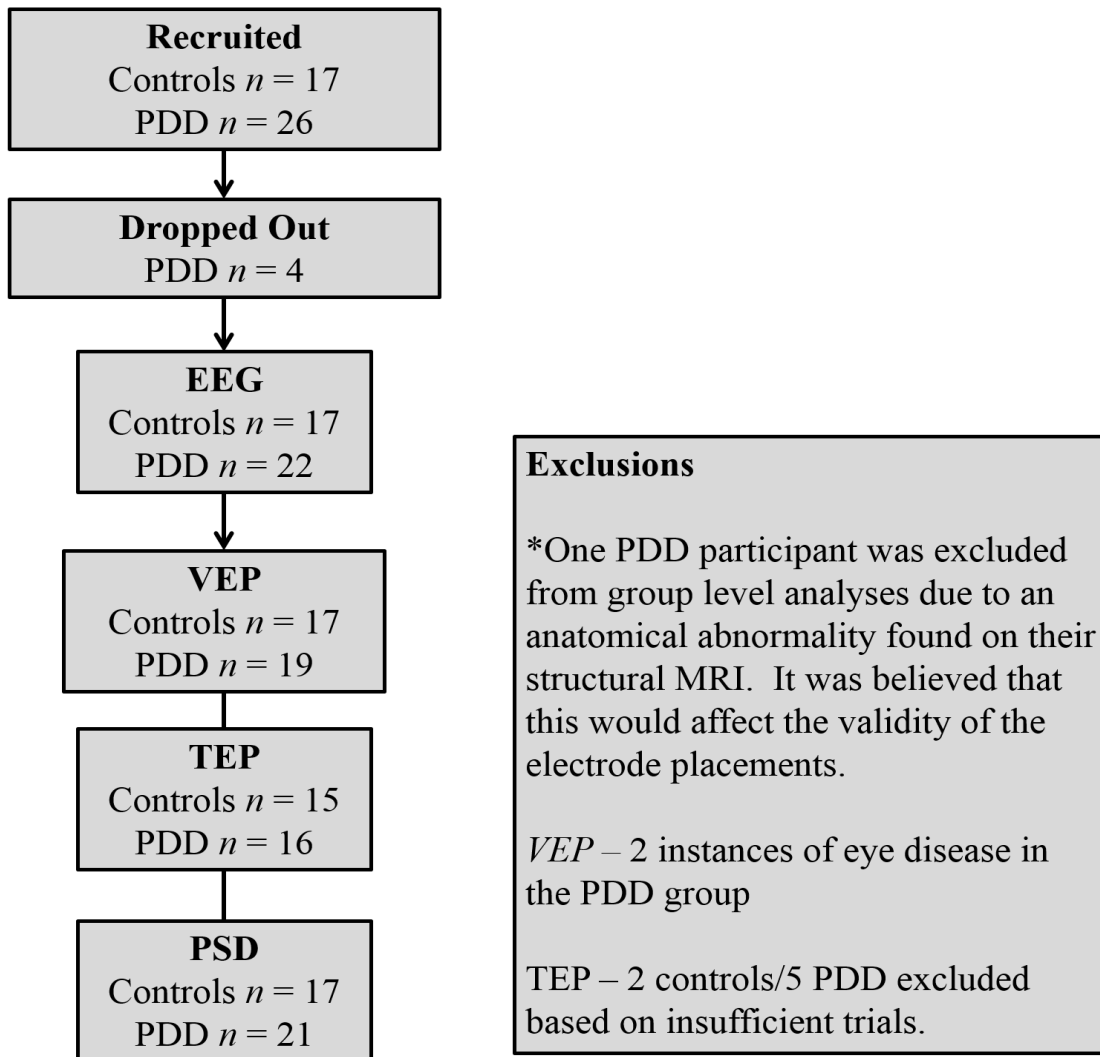


Figure 3.2, Flow chart depicting the number of participants included at each stage of the electroencephalography (EEG) analyses. Abbreviations: VEP – visual evoked potential; TEP – transcranial magnetic current stimulation (TMS) evoked potential; PSD – power spectral density.

Table 3.1, VEEGStim inclusion criteria, top: all participants; middle: controls specific; bottom: PDD specific.

Inclusion Criteria: General
<ul style="list-style-type: none"> • Age 60+ (either sex) • Provision of written informed consent or, if lacking capacity, consent provided by legal or other appropriate representative in accordance with provisions of the 2005 Mental Capacity Act • Absence of concurrent major psychiatric illness (e.g. major depression) • Absence of severe physical illness or comorbidity that may limit ability to fully participate in study • Sufficient English to allow assessment scales and cognitive testing
Controls
<ul style="list-style-type: none"> • MMSE>26 • Absence of memory complaints or signs/ symptoms of dementia and no prior history of visual hallucinations
PDD
<ul style="list-style-type: none"> • MMSE>12 • Meet criteria for probable DLB or PDD or PD-MCI If taking anti-cholinesterase drugs, memantine, anti-Parkinsonian medication – need to be stable for at least 3 months • Hallucinator group: Evidence of persistent, complex and recurrent visual hallucinations of a moderate to severe nature occurring in the 3 months prior to inclusion in the study • Non-hallucinator group: No evidence of recurrent, complex, visual hallucinations in the year prior to inclusion in the study • Presence of reliable informant sufficient to provide information for informant rated scales

Table 3.2, VEEGStim exclusion criteria, top: all participants; bottom: controls specific.

Exclusion Criteria: General
<ul style="list-style-type: none">• Skin allergies or sensitivities to electrode gels or any significant dermatological / scalp disease• Past history excess alcohol intake• Past history of other neurological illness including, but not limited to stroke, intracerebral pathology and epilepsy• Any metal or electronic implants which might be affected by strong magnetic fields (which occur in both MR and TMS-EEG component of study)• Psychotropic and other medications which may significantly interfere with cognitive & TMS-EEG testing (including but not limited to antipsychotics, sedative antidepressants, benzodiazepines except low dose when used as hypnotics or treatment for REM-sleep behaviour disorder, and centrally acting anticholinergic drugs)• History of moderate to severe visual impairment secondary to glaucoma, cataract, or macular degeneration
Controls
<ul style="list-style-type: none">• Past history of Parkinson's disease• Past history of visual hallucinations

Written informed consent was acquired from all participants with the capacity to do so (for information and consent forms see **Appendix 1**). In the case of a participant losing the capacity to consent, within the time frame of their involvement in the study, a consultee was identified and asked to determine the best course of action regarding the participants continued involvement in the study.

3.2 Baseline Testing

Clinical assessments were carried out, and baseline cognitive scores were acquired during the first visit, with all tests conducted at the participant's home. During this visit additional information about the participant's medical history, medication and disease status (if applicable) were collected. Items from the baseline testing that are applied in the analyses described throughout this thesis are outlined below.

3.2.1 Global Cognitive Function

Participant's global cognitive performance was primarily assessed through use of the mini mental state exam (MMSE; Folstein et al, 1975, maximum score = 30), which incorporates measures of recall, language, and awareness of time and location. More intact cognitive ability is reflected by greater scores. As a secondary measure the total score for the Cambridge cognitive test battery (CAMCOG; Roth et al, 1986; Roth et al, 1988; maximum score = 107) was utilised. This was intended as an extension of the MMSE and contains additional items for the testing of memory, language, attention, abstract thinking, praxis, perception, and numerical abilities. Measurements of visual and linguistic executive functioning were derived from the Trail Making task and fluency items on the executive and memory subscales of the CAMCOG.

3.2.2 Cognitive Fluctuations

The severity of cognitive fluctuations, as well as the quality of consciousness, was assessed using the clinician assessment of confusion and quality of consciousness test (CAF, Walker et al, 2000; maximum score = 16). This measure is completed by the carer and provides an insight into the frequency and severity of fluctuations in the past month.

3.2.3 Visual Hallucination Severity

Accounts of visual hallucination severity were recorded and scored using two measures allowing for a carer (Neuropsychiatric Inventory hallucinations subscale, NPI, Cummings et

al, 1994; maximum score = 12) and a patient (North East Visual Hallucinations Interview, NEVHI, Mosimann et al, 2008) perspective. The questions in the NPI hallucinations subscale are designed to measure the frequency (0 to 4), severity (0 to 3), and level of distress (0 to 5) of the VH. The product of the frequency and severity scores is used to quantify the extent of the VH experienced (based on the carer's accounts). In contrast the NEVHI is a semi-structured interview designed to investigate both the phenomenology of the VH and their impact on the patient's daily life. The interview provides separate ratings for the phenomenology, frequency of occurrence, and behavioural impact.

Although the NEVHI contains a separate battery of questions to gather a carer perspective it does not provide a single quantitative metric to describe, and/or categorise the experience of the individual relative to the experiences of others. However, although the NPI hallucinations subscale provides a more easily applicable metric it suffers a drawback in terms of content validity, failing to specifically account for VH, instead covering hallucinations (in any modality) more broadly. By comparison the NEVHI provides a very detailed account of temporal and phenomenological information relating to the experience of VH, with high interrater reliability (Mosimann et al, 2008; Bell et al, 2010). As a compromise in a previous TMS study the authors tested the validity of the NPI hallucinations subscale measure against ratings of VH taken from the patient NEVHI revealing minimal discrepancies between the two accounts (Taylor et al, 2011). To combat the drawbacks of the NEVHI, and to provide a quantitative comparison of the two measures an adhoc measure of the NEVHI score was created using the product of the scores from the sections describing frequency and duration (this is described in greater detail in **Chapter 4**).

3.2.4 Visual Perception

Visual Acuity: The integrity of the participant's visual acuity was assessed using LOGMAR (Logarithm of the Minimum Angle of Resolution) scale of visual acuity.

Motion Task: Motion sensitivity was tested by presenting the participant with a moving image at the top of the display (target object; see **Figure 3.3**) and two identical images moving at different speeds to each other. The participant was asked to select which of the two images matched the speed of the target object.

Angle Task: The minimum detectable angle was assessed by presenting a target object consisting of two adjoined lines, at the top of the screen (see **Figure 3.4**) and two similar items below. The participant was asked to match the target object to the item which had the two lines oriented at the same angle as in the target item.

In both of these tasks a staircasing procedure is implemented which increases the difficulty of the task (greater similarity between speeds and angles) in accordance with a string of correct responses, and decreases the task difficulty with more incorrect responses. The aim of this is to eventually reach a difficulty that reflects the minimum difference in speed or angle that the participant can detect. Tests of motion and orientation sensitivity were included on the basis that space and motion perception in LBD are the most prominent visual perceptible disturbances, and have utility in distinguishing between those with and without VH (Mosimann et al, 2004). Whilst these have been attributed to ventral system pathology (see Mosimann et al, 2004) there is not currently any literature concerning their relationship with synaptic communication during active visual processing throughout the dorsal and ventral systems.

Pareidolia Task: Pareidolia are false positive reports of images apparent within a display that contains a high level of noise. For example, the distribution of colour and shading on an image of a flower might cause the contours on a petal to be interpreted as a face. Thus, pareidolia reflect an individual's ability to correctly discern signal from noise. In the current study the participants viewed a series of black and white images and were asked if an image had been present amongst a "noise" display (see **Figure 3.5**), during some trials a face would be embedded within the image, whereas on others there would be only the noise stimulus. The participant was asked to point to where they had seen an image; false perceptions were noted as instances of pareidolic imagery. The frequency of false positive reports of stimuli within a distorted image (pareidolia, e.g. Uchiyama et al, 2012) was used as a measure of higher visual perception. Pareidolia have previously been shown to relate to the severity of VH, and demonstrated a reduction in frequency following treatment with donepezil (Yokoi et al, 2014). This suggests that pareidolia have a utility for inferring the integrity of the cholinergic system in aiding the communication of ventral and primary visual regions for separating out salient features of an image.

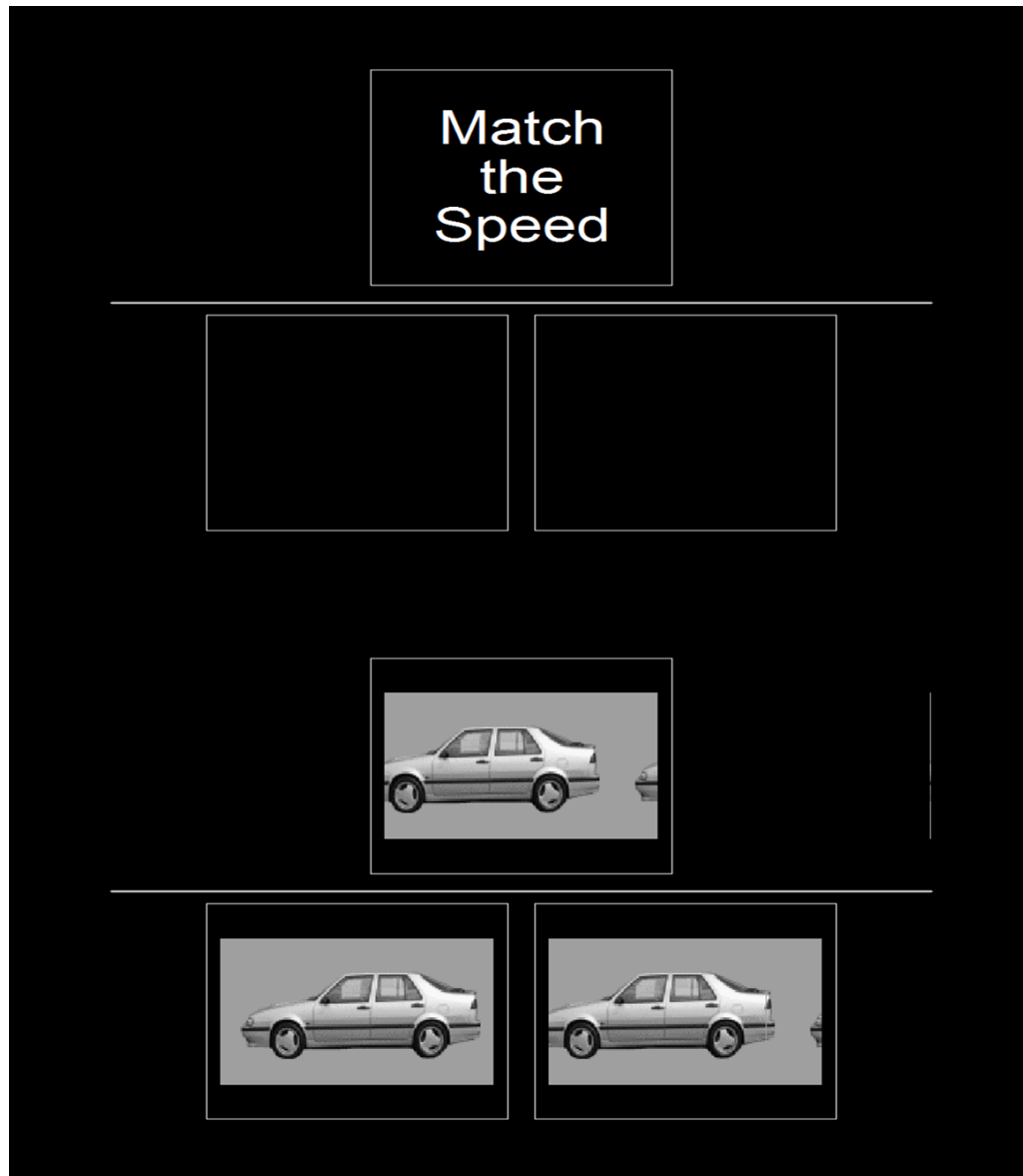


Figure 3.3, The display presented to the participants during the motion task. Top) The task instructions. Bottom) The participant was tasked with matching one of the bottom cars with the top car based on their speeds.

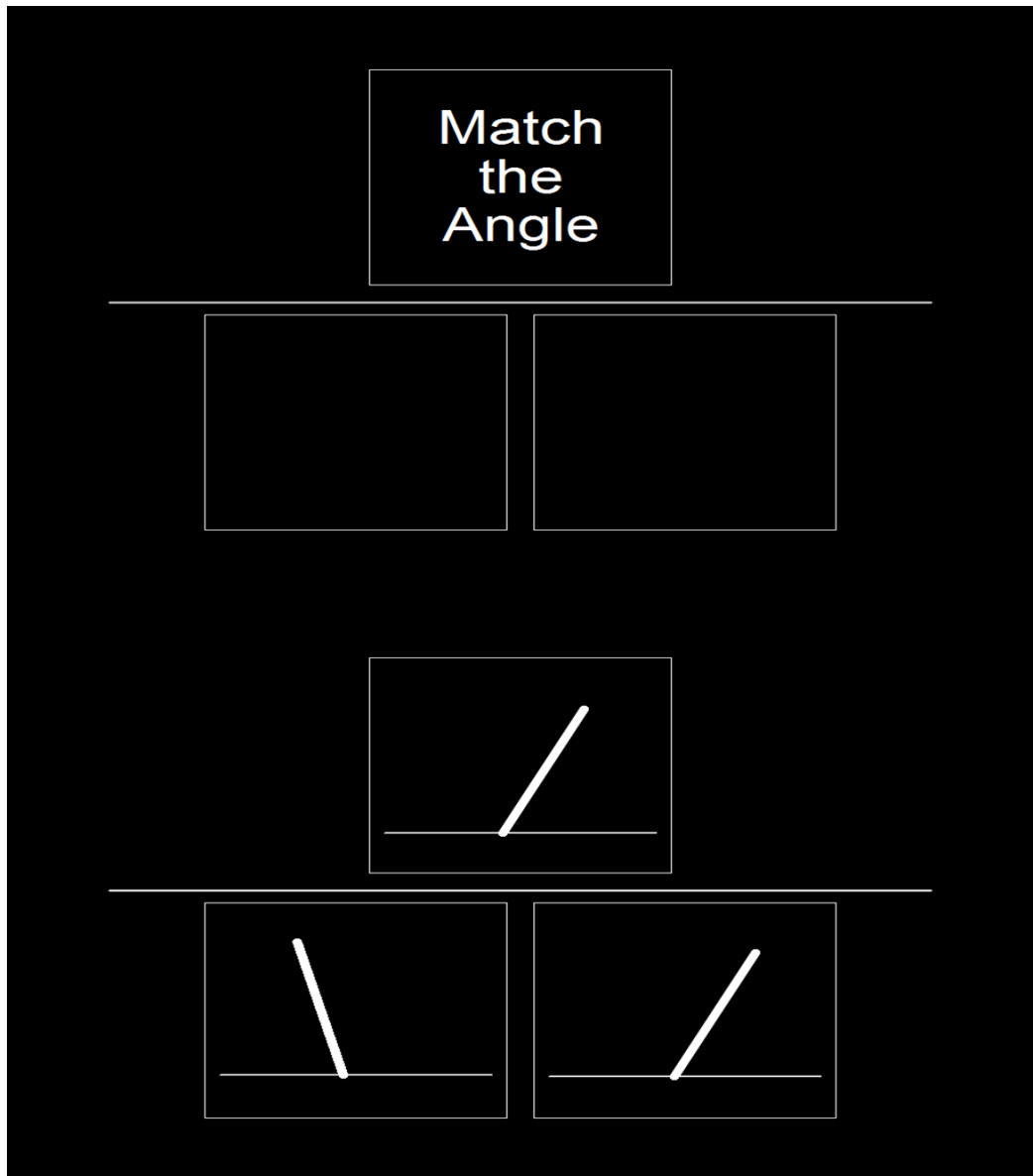


Figure 3.4, The display presented to the participants during the angle task. Top) The task instructions. Bottom) The participant was tasked with matching one of the bottom lines with the line in the top frame based on their angle.

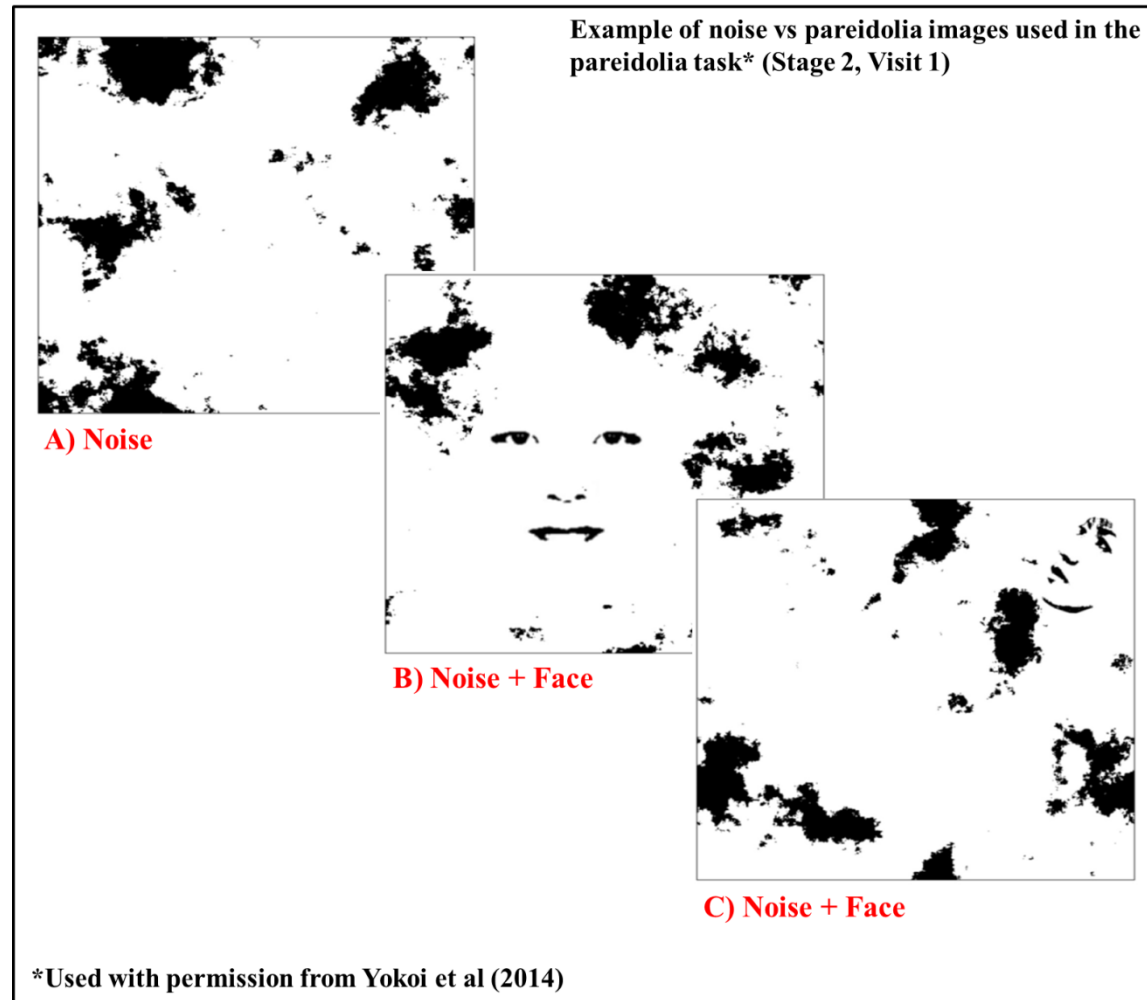


Figure 3.5, An example of the stimuli presented to the participant during the pareidolia task. Each trial either contained a “noise” display or a “noise” and face combination. Participants were asked if they had noticed any images within the display and to point to them, a pareidolia was noted when the participant reported seeing an object that was not actually present within the “noise” display.

3.2.5 Motor Ability

Overall severity of motor symptoms was assessed using section three of the unified Parkinson's disease rating scale (UPDRS), which covers dexterity of extremities, motion of the face and neck, speech, vertical motion, posture, gait, tremor, and speed of motion. Higher total scores indicated more severe motor symptoms.

3.3 Equipment

All equipment listed below, and used in the studies described within this thesis met with British (BSS5724) and European (EEC; EN60601-1) safety standards for medical devices.

3.3.1 Electroencephalography Recordings

Electroencephalography (EEG) was recorded using an ASA-LAB 136 system amplifier (see **Figure 3.6A**) and the ASA-LAB recording software (version 4.9.1) in combination with a 128 Ag/AgCl channel Waveguard cap (Advanced Neuro Technologies; see **Figure 3.6B**), and a clavicle mounted ground electrode. To ensure that all scalp recordings were accurately and validly measuring electrical activity from the same sources three different size caps were available to account for differences in head circumference (small: 47cm to 51cm; medium: 51cm to 56cm; large: 56cm to 61cm). All recordings were performed using a 128 channel montage based on the 10-5 electrode placement system (Oostenveld & Praamstra, 2001), and referenced to the electrode Fz. Electrode impedance was reduced to less than 5k Ω , and no filters were applied during EEG acquisition.

3.3.2 Transcranial Magnetic Current Stimulation

Stimulation was delivered using a Magstim 70mm figure of eight coil connected to a monophasic Magstim 200² stimulator (The Magstim Company LTD, Dyfed, Wales; see **Figure 3.6C**). The figure of eight coil was chosen due to the enhanced focality created by the orientation of the two windings (Walsh & Pascual-Leone, 2003). Pulse delivery was controlled using the coil mounted switch, with a maximum stimulation rate of 0.1Hz. After each pulse a trigger was sent to the ASA-LAB software to mark the timing of the event and using an interface module (see **Figure 3.6D**).

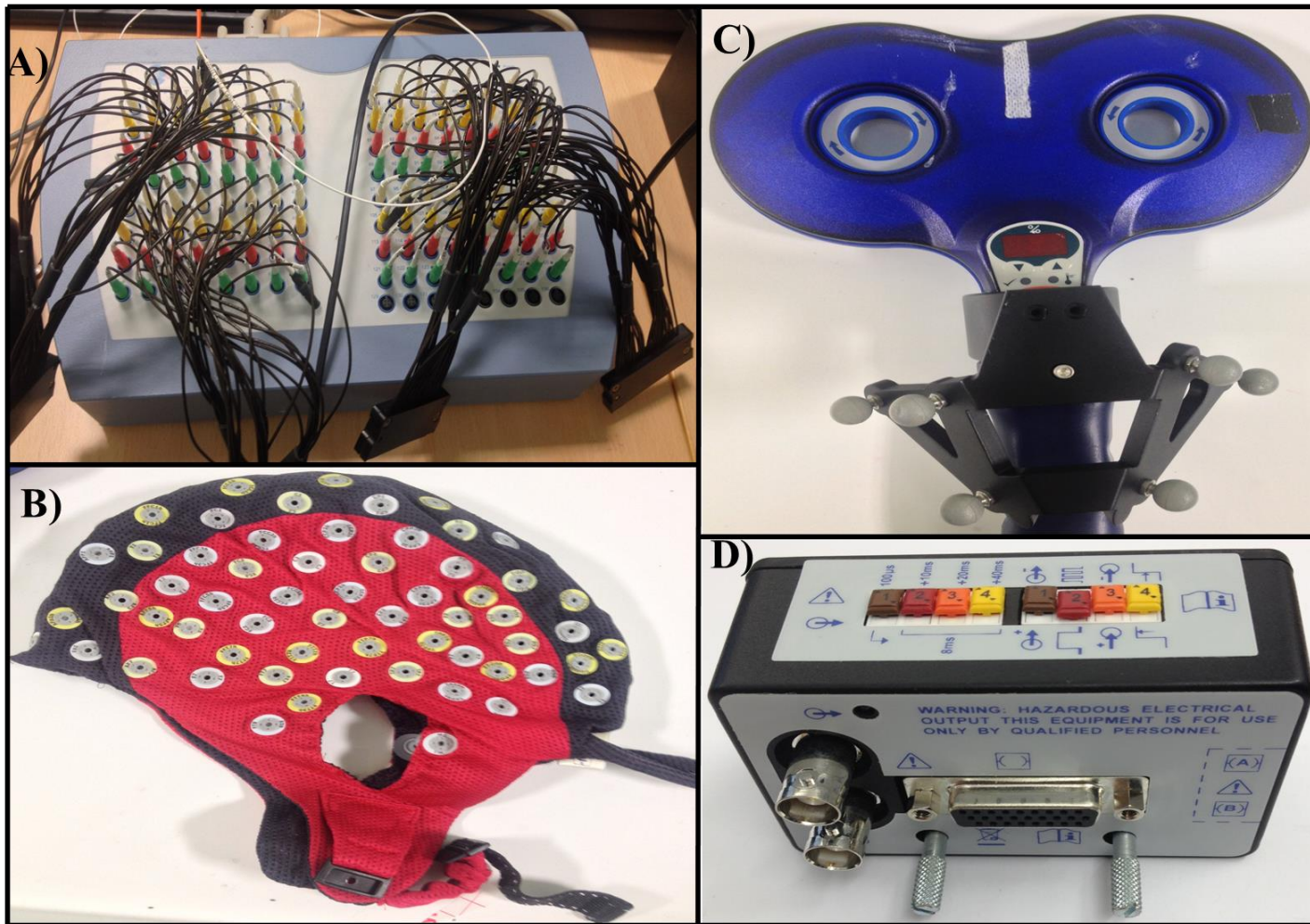


Figure 3.6, A) ASA-LAB 136 system amplifier. B) 128 Channel Waveguard electroencephalography (EEG) cap; C) Figure of eight, hand controlled transcranial magnetic current stimulation (TMS) coil with neuronavigation attachment. D) TMS-EEG interface module.

Between trials reliability of the coil placement was managed using a Visor2 stereotactic navigation system (Advanced Neuro Technologies, Amsterdam, Netherlands; see **Figure 3.7**). This uses the participant's structural MRI (collected in visit 2, see **Figure 3.8**) as well as information about the shape of the participant's head (collected from markings placed on the scalp), and the position of the coil to provide a computerised marker of each TMS pulse's coordinates. The coordinates were then translated into MRI space and presented above their rough spatial location on the cortex (see **Figure 3.8**). The Visor2 navigation software (version 2.1) was run using a Hewlett Packard (HP) Compaq elite 8300 (Microsoft Windows 7), and presented on an HP Compaq LA2405x 24 inch LCD monitor (resolution: 1920 x 1200 pixels, refresh rate: 60Hz).

3.3.3 Stimulus Display

Software for the running of the VEP and TMS paradigms (see below) was managed using Matlab (version 12a, The Mathworks, 2012), run on a Dell OptiPlex 755 (Microsoft Windows XP) and presented using a Dell U2412M 24 inch LCD monitor (resolution: 1920 x 1200 pixels, refresh rate: 60Hz). To ensure that triggers from the reversal of the VEP stimuli were accurately placed relative to the start of the event a photodiode was used to measure the delay between the stimulus being generated at the computer and presented on the monitor. The photodiode was placed over a single check within the display and recorded for 200 reversals. The photodiode recording demonstrated a consistent stimulus onset time of 0.39ms (\pm 0ms).

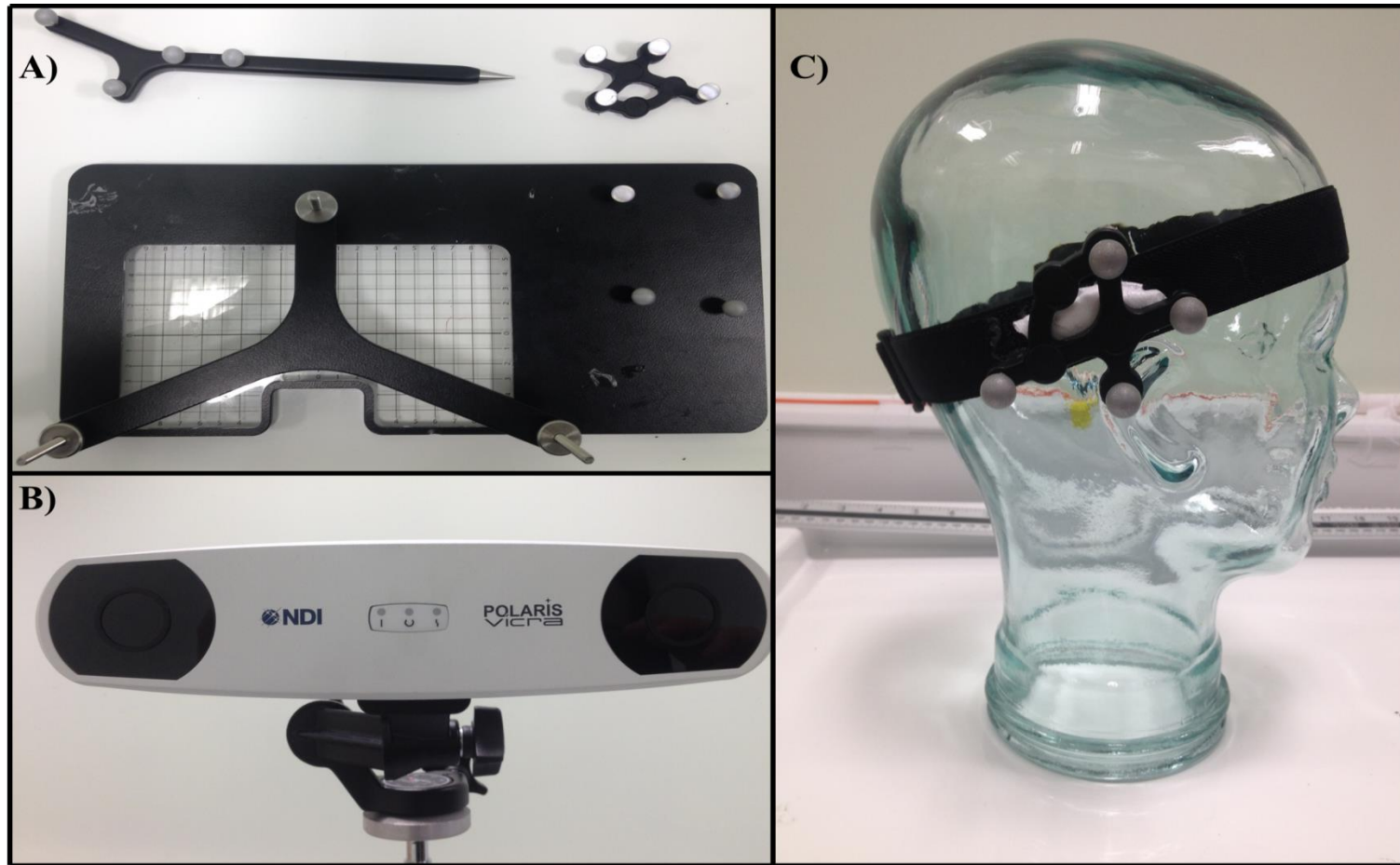


Figure 3.7, The equipment used for TMS neuronavigation (ANT VISOR2). A) (left to right, top to bottom) Stylus for marking co-ordinate locations; reflective reference device for locating the participant's head; calibration board for determining the centre point of the transcranial magnetic current stimulation (TMS) coil. B) Polaris Vicra infrared camera used to detect light emitted from the reflective surfaces of the items in (A). C) Placement of the scalp reference device.

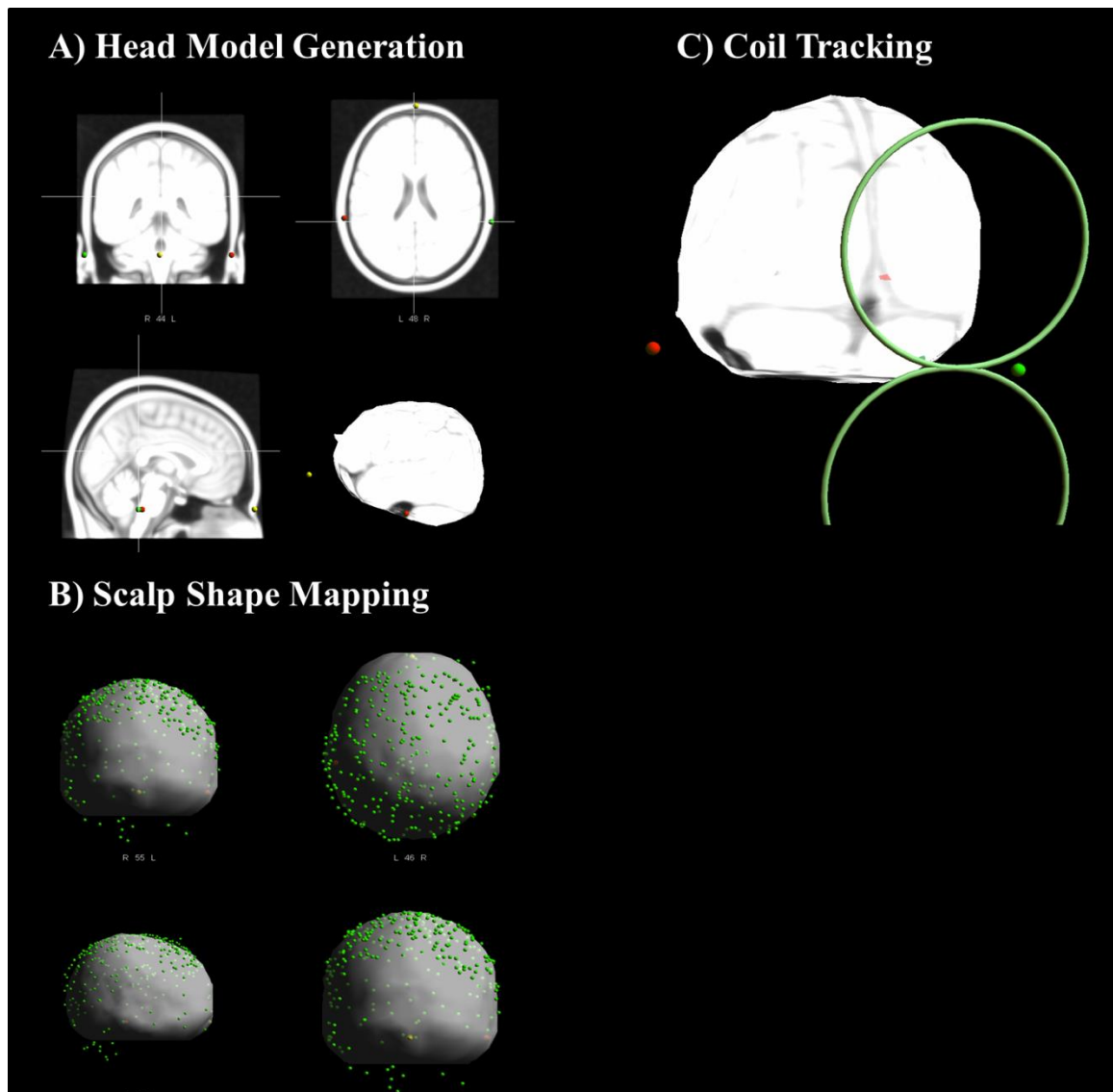


Figure 3.8, Stages required for setting up the neuronavigation. A) A three dimensional head model is created from the T1 structural magnetic resonance image (MRI). B) Co-ordinates are placed on the scalp to help map its shape to the three dimensional head model. C) Demonstration of the display used for tracking the transcranial magnetic current stimulation (TMS) coil.

3.4 Electrophysiology Protocol

All electrophysiology tasks were performed during Stage 4 of the VEEGStim study structure (see **Figure 3.1**), with a typical running time of 150 minutes. During the session the participant was sat upright, and the light levels were varied to suit the demands of the task. Each task was separated by a rest period of several minutes, and breaks were provided regularly during the TMS task to prevent fatigue and light adaptation (see below). Participants were requested to limit their movements so as to help reduce artefacts in the recordings.

3.4.1 Resting State Electroencephalography

EEG Activity was recorded during two resting conditions (eyes open & eyes closed) allowing for the comparison of posterior spectral patterns in response to eyes closing (see **Chapter 7**). During the eyes open condition the participant was asked to look at the centre of the blank computer monitor in front of them to prevent movement related artefacts and confounds related to orienting of attention to objects in the environment.

3.4.2 Visual Evoked Potential

Pattern reversal visual evoked potentials were acquired by presenting the participant with a checker board pattern (individual checks with a visual angle of 0.6°) that was phase reversed every 500ms, with a total of 200 trials. At the start of each presentation a trigger was delivered to the ASA-LAB software to mark the beginning of a new event. The monitor was viewed from a distance of one metre and adjusted so that the centre of the display, marked by a pink focus point, was at the participant's eye level. During the recording participants were requested to fix their gaze on the focus point to prevent eye wandering.

To determine potential markers of undiagnosed eye disease three separate recordings were performed, covering the stimulation of the left and right eyes individually as well as together. The procedure for checking interocular differences and its impact on the analysis is described in **Chapter 5**. During the individual eye conditions stimulation of the unattended eye was prevented by covering the eye using a hypoallergenic, adhesive eye patch (3M Opticlude Orthoptic eye patches, 5.7cm x 8cm).

3.4.3 Transcranial Magnetic Current Stimulation & Phosphene Elicitation

Stimulation was performed by placing the coil windings at the occipital cortex in a rostrocaudal orientation (see **Figure 3.9A**) as this orientation has previously demonstrated the ability to enhance phosphene occurrence for a given level of stimulation intensity (e.g.

Kammer et al, 2001). During the TMS task the lights were dimmed and the participant was requested to close their eyes whilst wearing an eye patch over each eye (see above). In previous studies this approach has aided the perception of phosphenes by reducing distractions and helping to focus the participant's attention (e.g. Marg & Rudiak, 1994; Taylor et al, 2011). The aim of its use in the current study was to reduce the chances of the participant becoming distracted by items in the environment and to also minimise the likelihood of false positive reports. Furthermore, by maintaining a state of having eyes closed the likelihood of blinks and ocular motion within the EEG data was drastically reduced. However, the short and often subtle appearance of phosphenes means that it can take many pulses before a participant is confident in reporting both their presence and phenomenology (Marg & Rudiak, 1994). To improve confidence in phosphene reporting the experiment began with a short adaptation session (see below). The caveat to performing stimulation whilst the participant remains in darkness is that even short periods of light deprivation can alter the excitability of the visual cortex neurons (Boroojerdi et al, 2000). The typical time period for this in healthy adults is approximately 45 minutes, with the effects lasting up to 120 minutes after re-exposure to daylight levels of luminance (Boroojerdi et al, 2000), although this has not been studied in an ageing or clinical population meaning that the time limit for light adaptation in the ageing and PDD populations is unknown. To avoid light related confounding features the participants were exposed to daylight levels of luminance every fifteen minutes for several minutes before continuing with the study.

The mechanisms of phosphene generation remain poorly understood; however, despite individual differences in stimulation location and threshold those who respond to phosphenes share the common factor of a "sweet spot". This is the location at which phosphenes can be reliably reported with greater intensity and at a lower level of stimulation than other sites. The optimal site for describing phosphenes was determined by applying TMS at sites on a hypothetical grid equal in size to 10% of the vertical scalp distance (inion to nasion via the midline) and 20% of the horizontal distance (inion to nasion via the lateral portion of the scalp). Stimulation began at Oz and was moved vertically in instances of 5% until reaching electrode POz. In the case that phosphene perception could not be achieved along the midline the same procedure was repeated at locations 5% laterally until the electrodes at 10% of the horizontal distance (in either direction) had been tested. Intermediate measurements were done by placing the centre of the coil midway between two electrode locations and then measuring the distance between the current and previous locations to determine that this matched the desired percentage of the inion to nasion distance (horizontal or vertical).

At each site a series of ten pulses, separated by at least ten seconds, were first applied using 75% of the stimulators maximum output. If consistent phosphene perception (70% of trials or more) was not successful the output was increased in increments of 10% until either a consistent response was achieved or the stimulator output had reached 100% and a different position was selected. Once a consistent response had been achieved the stimulator output was reduced in increments of 5% until the participant only reported phosphenes on 50% of trials (e.g. Taylor et al, 2011; Marg & Rudiak, 1994; Kammer et al, 2005; Taylor et al, 2010). In the case that phosphene perception abruptly stopped, or was much lower than 50% of trials the process was repeated at other sites until this could be achieved. Participants who did not experience phosphenes at any site were subsequently stimulated at Oz using 75% of the stimulator output. In a number of participants phosphenes were only experienced very infrequently. Partial responders were treated the same as phosphene responders, but were only included in the phosphene vs no-phosphene TEP analysis if there was a sufficient number of phosphene responses.

During the EEG recording pulses were delivered in blocks of 20, containing a minimum of one sham trial to help monitor the occurrence of false positive reports (e.g. Taylor et al, 2011), after each trial the participant was asked if they had seen a phosphene. Sham trials were performed by positioning the coil as normal and tilting it to remove the centre surface whilst retaining contact between the scalp and the upper winding (see **Figure 3. 9B**), because the strength of the field dissipates exponentially with the distance from the coil the stimulation from the pulse at both the centre and the winding would not be strong enough to depolarise the local axonal bodies. Participants received a total of $n = 240$ real pulses and $n = 15$ randomly placed sham trials. After finishing the stimulation protocol all participants who had perceived phosphenes were asked to provide a phenomenological account of their “average” phosphene experience. To determine the crude complexity of the average percept this experience was measured by noting instances of phenomenology using a scale based on the complexity scale used in a previous report (Taylor et al, 2011). Particular importance was placed on: shape, colour (including polychromacy), motion, luminance, and the presence of visual hallucination like features (e.g. faces, animals, objects). The questionnaire used to report phosphene phenomenology is provided in **appendix 2**.

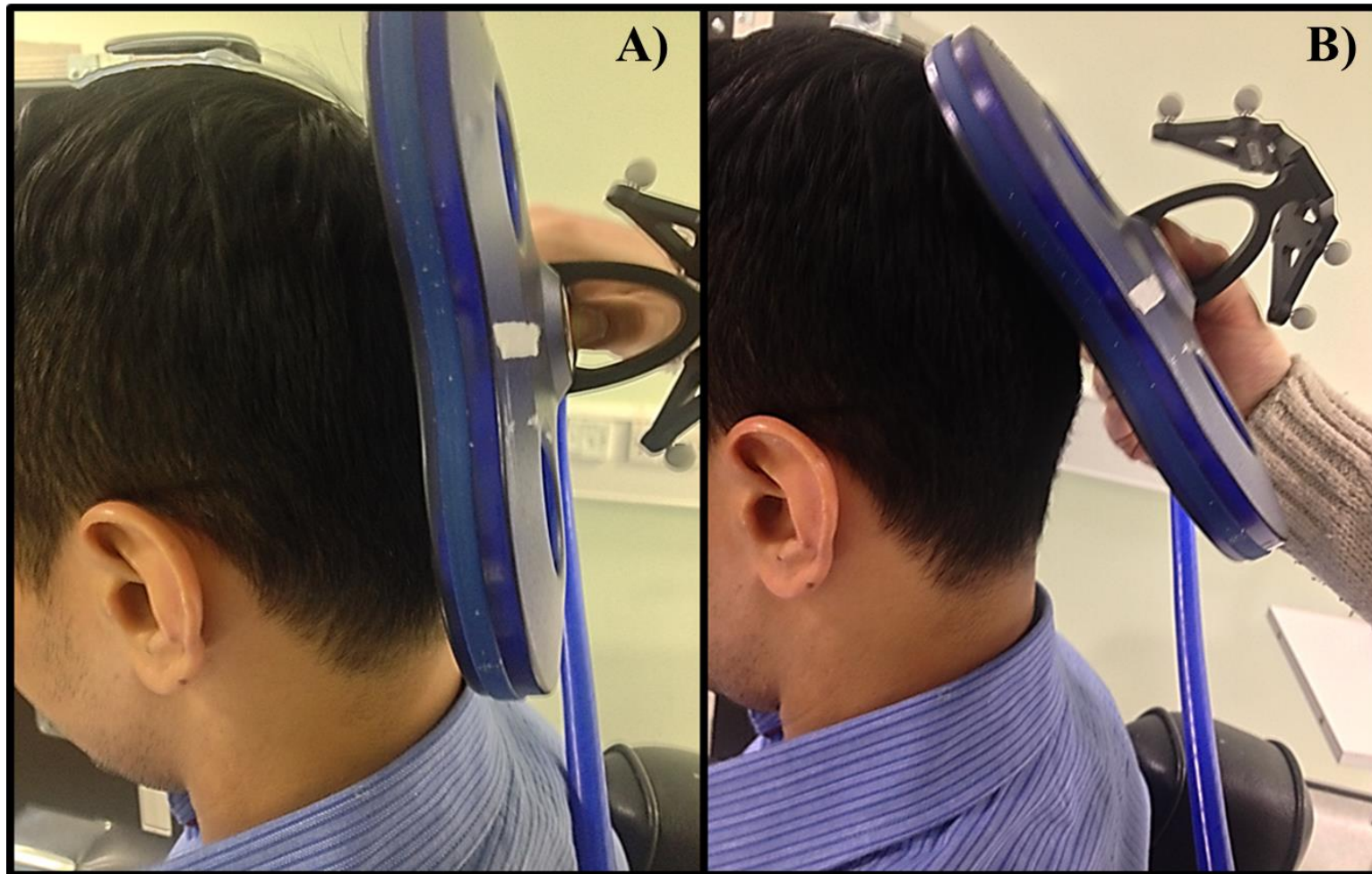


Figure 3.9, Demonstration of the differences between active (A) and sham (B) coil positioning. During sham trials the coil is gently positioned so that only the upper winding is still intact with the scalp, this prevents active stimulation of the region of interest and is useful when wanting to identify false-positive reports of phosphenes.

3.4.4 State Monitoring

All PDD participants were tested during a motor “on” state and were allowed to take medications as appropriate throughout the duration of the study. Variations in motor function were monitored at several intervals during the electrophysiology session using the hand, finger, and leg movement items from the UPDRS section three.

It was expected that a certain number of PDD participants would be taking cholinesterase inhibitors (ChI) for the treatment of cognitive fluctuations and more severe global cognitive impairment (Wang et al, 2015; Rolinski et al, 2012; Aarsland et al, 2004) as these are a common feature of PDD (Aarsland et al, 2007; Aarsland et al, 2004). The prevalence of ChI in this sample is described in **Chapter 4**, and their potential effects on different elements of the acquired data are discussed in their respective chapters (see **Chapter 6 & Chapter 7**). In all PDD participants the general level of arousal was monitored at regular intervals using a visual analogue scale. The participant was asked to point to the position (labelled 0 to 10) on the scale which best described how alert they currently felt, with higher scores indicating higher arousal. Participants who reported intermediate to low (≤ 5) levels of arousal were provided with a short break and then asked how well they felt that they would be able to perform on the remainder of the task. If the participant felt unable to confidently continue with the task at hand the session was terminated.

3.5 Data Analysis

The pre-processing and analysis of EEG data was performed using Matlab (version 12a, The Mathworks, 2012), the EEGLAB toolbox (Delorme & Makeig, 2004), and the ERPLab toolbox (Lopez-Calderon & Luck, 2014). Group level comparisons were performed using the Statistical Package for the Social Sciences (SPSS, version 22, IBM Corp, 2013, Armonk, NY). The procedures described below are generic processes that were implemented across each (or most) of the individual analyses; details of analyses specific to the different studies are described in their respective chapters.

3.5.1 Electroencephalography

Pre-Processing

The raw EEG data contains a mixture of cortically generated information as well as noise picked up from both the participant and the environment (such as electrical interference). Before it is possible to make inferences regarding event related or spontaneous neural activity a suitable signal to noise ratio needs to be obtained so that the neural activity of interest can

be visualised reliably and validly (e.g. we can be certain that the activity being measured is cortical and not influenced by external sources).

Filtering

By filtering the data it is possible to attenuate the contribution of signals with undesirable frequencies. For example, sweating causes the potential of the skin to gradually rise which is manifested as a slow increase in the amplitude of the EEG signal at a given channel over time (delta band, 1-3Hz). This particular artefact can be attenuated by using a high pass filter; this provides a cut off below which the contribution of that frequency range is removed (e.g. a cut off of 4 Hz). The opposite of this approach can be used to attenuate the contributions of higher frequency data such as muscular activity. However, when applying a low pass filter there is a greater chance that the data beyond the cut off will also contain cortical information and thus greater care should be taken when selecting the frequency range of interest whilst trying to limit the contributions of artefacts.

In all of the analyses described the data were treated with a band-pass filter providing high and low frequency cut-offs, and the specific limits used are described in the subsequent chapters. To prevent the latency distortions that can be caused by the application of traditional filtering models (Luck, 2005, Ch. 5) the filter design implemented the Matlab zero-phase filtering tools (Gustafsson, 1994), which correct for delays by running the filter in both directions across the data (Wildmann et al, 2015).

Artefact Removal

The majority of EEG artefacts were controlled for by asking the participants to remain still for the duration of the recording (in between breaks where appropriate), and to focus their gaze on the monitor in front of them. Epochs/sections of the data containing blinks, muscular activity (EMG), or slow drifting potentials caused by sweating were identified and removed using independent components analysis (ICA; Jung et al, 2000; see **Figure 3.10**) where possible, and removed from the data using manual trial rejection when ICA was not implemented (or failed to estimate a stable representation of the artefacts). Independent components analysis (ICA) is a method of blind source separation (BSS) that estimates a series of statistically independent, non-Gaussian sources based on the input data (see **Figure 3.11**; Hyvärinen et al, 1999; Hyvärinen, 1999; Hyvärinen & Oja, 2000; Makeig, et al. 1997; Hyvärinen, 2001). Independent components analysis was chosen as a method of artefact detection, and removal, to prevent removing large numbers of trials (or segments of

continuous data) from noisy data which would potentially bias the data by severely limiting the number of trials available for averaging (see **Figure 3.12** for an example of artefact detection and removal using ICA). Figure 12 demonstrates the use of ICA for identifying electrical and muscular artefacts in resting state EEG data whilst discriminating this from cortical activity. This was achieved using the PSD estimate of the analyses sources; the topographies of the weights associated with each source as a visual determinant of their spatial information; and the time course associated with each source. The final (**Figure 3.12 C**) panel shows the mixed data PSD with the removal of the 50Hz electrical artefact, and a reduction in the extent of beta activity related to EMG muscular activity. Eye blinking, that is usually a common source of noise in EEG was not present as a major artefact across the dataset due mainly to their being a tendency for the paradigms to require the closing of the participant's eyes (except for the VEP and eyes open resting state).

In terms of principles, from an ICA perspective, the EEG data (X) is a matrix of signals with n time points (t), where $X(t)$ depends on the signals coming from the brain sources (S). ICA estimates the unknown mixing matrix (W), that depends on the position and nature of the sources in the brain and their distances from the recording electrodes (Nunez and Srinivasan 2006). To estimate the independent sources of the recorded activity the mixed signal ($X(t)$) is multiplied by the inverse of the mixing matrix (W^{-1}). The output of this process is a matrix containing the estimate of the sources, as derived by un-mixing the signals from the electrodes, and the mixing matrix. The unwanted components can be removed and the process reversed to reassemble the data without the artefact sources. The FASTICA algorithm (Hyvärinen & Oja, 1999) was used to help detect and reduce the presence of artefacts in the analysis of the resting state data (**Chapter 7**) and the TMS evoked potentials (**Chapter 6**).

In some instances individual EEG channels showed high impedance from poor scalp contact (a limitation of using a cap rather than individually fitted electrodes). These channels were removed before all other processing and recreated using spherical interpolation after remaining data had been processed (Perrin et al, 1989; Ferree, 2000; Delorme & Makeig, 2004). Fully processed data was then converted to the common average reference before extracting individual measurements.

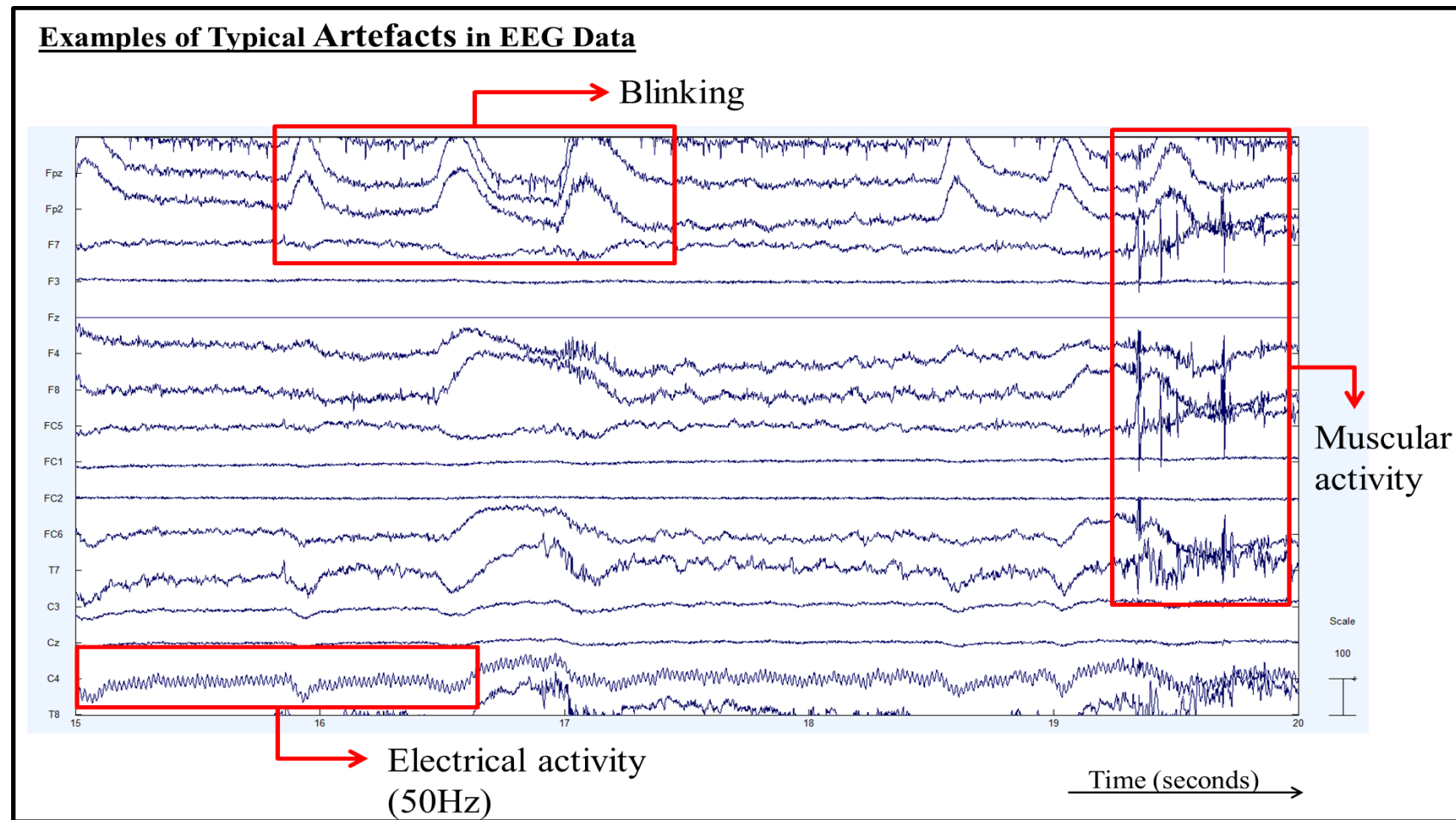


Figure 3.10, An example of common electroencephalography (EEG) artefacts: blinking, electrical mains 50 Hz oscillations, and muscular (electromyography, EMG) activity.

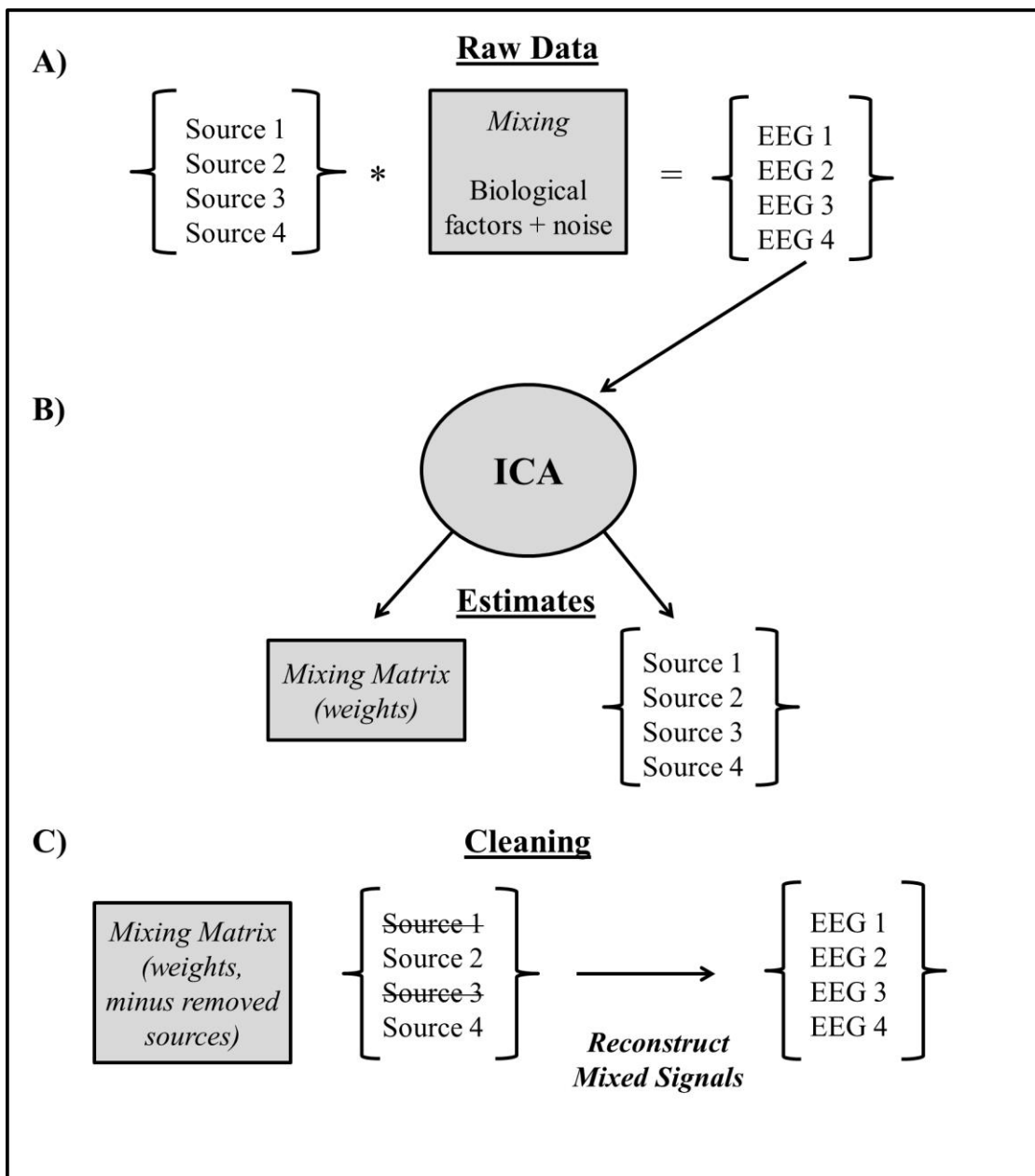


Figure 3.11, Schematic illustration of the use of independent components analysis (ICA) for the cleaning of electroencephalography (EEG) data. A) The EEG data represents a mixing of the original sources by factors such as orientation, cortical tissues, the skull & meninges, as well as external sources of noise such as mains activity (50Hz). B) ICA estimates the original sources and the parameters of their mixing. C) Unwanted components can be removed and then recombined using the mixing matrix to reconstruct the EEG data without the artefactual sources.

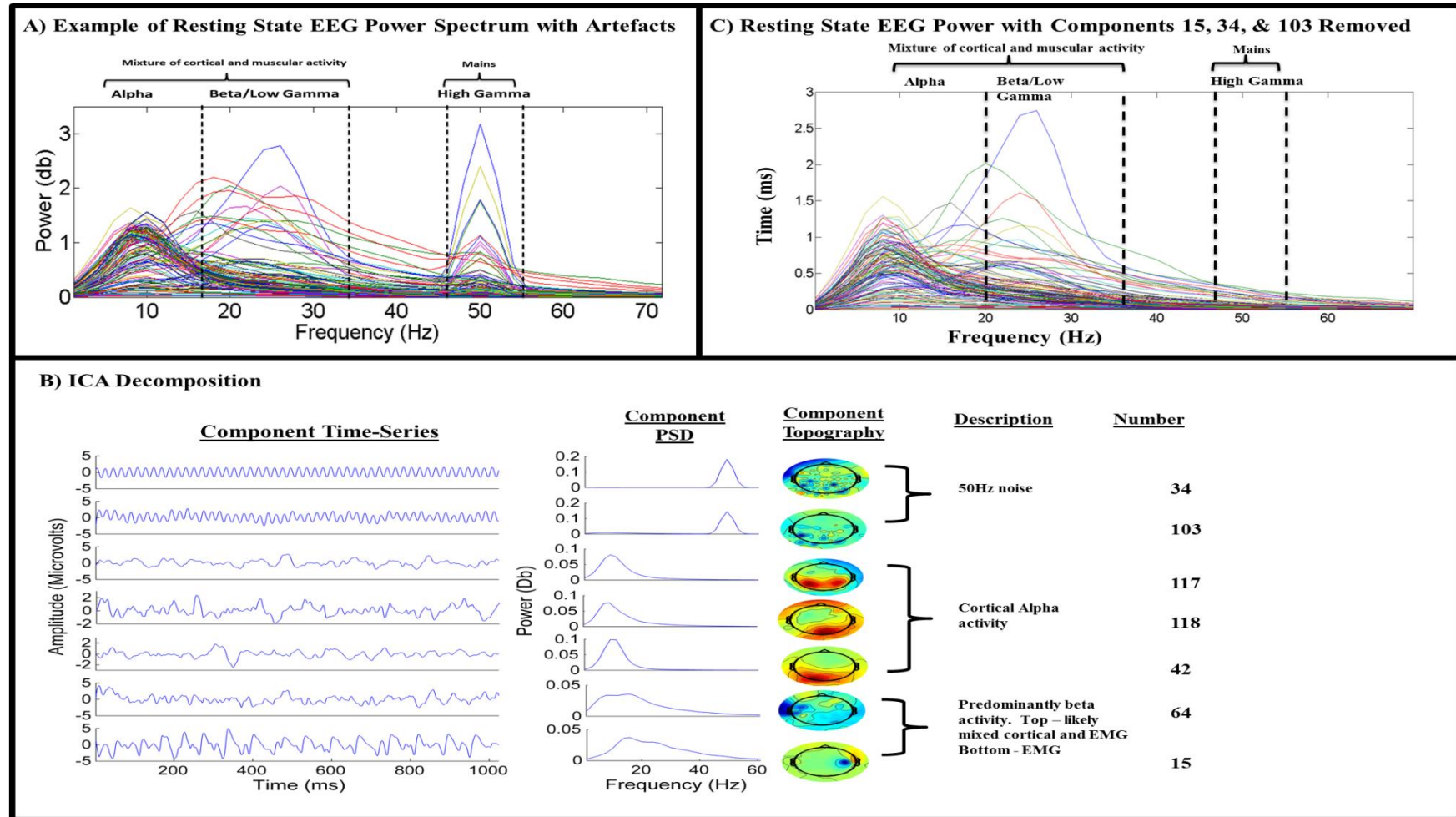


Figure 3.12, An example of the use of independent component analysis (ICA) to identify and remove electrical and muscular artefacts from resting state electroencephalography (EEG data). A) Resting state data power spectrum with artefacts (muscular and mains noise). B) Results of ICA displayed using component time series, power spectrum density (PSD), and topographic maps. C) Resting state EEG data power spectrum with artefacts removed.

Epoching and Measurement

The cortical response to specific events was studied by averaging together segments of the data containing evoked changes in the signal potential over a given period of time. Each epoch was set to a specific length of time based on the known or expected latency of key processing components that were evoked by the stimulus. This period was preceded by a resting period that was used to subtract trends from the data and maintain a mean of zero (baseline correction).

The amplitude and latency of the evoked potential components were measured using different temporal windows defined by the peaks in the participant's global field power (GFP) for each recording. The GFP is a reference-independent measure of topographic activity and helps with identifying when in time there are prominent periods of activity across the scalp (Lehman & Skrandies, 1980). This is estimated as the root mean square of the average referenced data (all channels) at each point in time for the grand average dataset (see **Equation 3.1**).

$$GFP(t) = \sqrt{\frac{\sum_i^k (V_i(t) - V_{mean}(t))^2}{k}}$$

Equation 3.1: Calculation of the global field power as in Lehman & Skrandies (1980). t is the current time point, k is the total number of channels, i is the index of the current channel, and V_i is the voltage of the current channel.

Removing Transcranial Magnetic Current Stimulation Artefacts

Magnetic pulse artefacts are a concomitant feature of combined TMS & EEG recordings, and raise significant challenges in terms of data analysis due to their complex nature and tendency to severely lower the signal to noise ratio of the EEG data. Due to the substantial degree of noise it is difficult to accurately determine the underlying TMS evoked potentials (TEP), requiring several stages of additional pre-processing to improve the signal to noise ratio. In recent years there has been a plethora of suggestions for hardware (Taylor et al, 2008; Illmoniemi & Kičić, 2010), software (Morbidi et al, 2008; Thut et al, 2005), and even physiological manipulations (e.g. epithelial micro-punctures, Julkunen et al, 2007) that can improve the quality of the data and allow for more accurate, "artefact free" measurements. However, there is currently no gold-standard consensus for an artefact removal procedure and

little knowledge of how to ensure that the subsequent measurement retains a high degree of validity (Murphy et al, 2015).

During EEG recording the application of the TMS pulse to the scalp causes the signal to rapidly shift in potential, the signal then shifts polarity (appearing to oscillate) for several milliseconds before making an exponential return towards the baseline (taking up to several hundred milliseconds, referred to as a decay effect). During rostrocaudal occipital stimulation the placement of the windings near to the cranial muscles can cause twitching of the scalp and neck leading to muscular artefacts appearing within the epoch; however this can be reduced or prevented by placing a hand over the cranial muscles to defend from the pulse emitted by the extremes of the coil windings. This is made possible due to the exponential decay in the pulse strength with the distance from the coil.

Due to its complexity, it is not yet possible to efficiently remove the artefact occurring immediately after the pulse without the application of methods beyond the scope of this thesis (e.g. Kalman filters, Morbidi et al, 2008), and so it is replaced using linear interpolation between 0ms and 20ms (see **Figure 3.13**; Assecondi et al, 2013). The remaining decay and muscular artefacts are less complicated, sharing properties with similar artefacts found in typical EEG data (such as slow wave sweat induced potentials, and EMG from head motion, e.g. Jung et al, 2000), and as such can be reliably identified and removed from the data using ICA, without affecting the profile of the cortical response (the TMS evoked potential, TEP; Korhonen, 2010; Korhonen & Illmoniemi, 2011; Rogasch et al, 2014; Murphy et al, 2015; Illmoniemi et al, 2015; Winkler, Haufe, & Tangermann, 2011).

The advantages of ICA over the use of subtraction or regression based methods (Thut et al, 2005) are that it is possible to separate functionally distinct sources with ICA (Jung et al, 2000; Korhonen et al, 2011), and that the amount of cortical activity removed is limited (Jung et al, 2000; Makeig et al, 1996). However, it is worth noting that ICA only estimates the sources of activity and is not a perfect way to separate out data. Whilst the accuracy will improve with a larger number of data points, it is possible for the source estimates to contain mixing of activity (artefact and cortical sources) when the data contains a high number of channels (defined as overlearning, see Korhonen & Illmoniemi, 2010; Hyvärinen et al, 1999; Särelä & Vigário, 2003). Therefore, removing independent components should be done sparingly to prevent the excess removal of cortical activity incorporated within the artefactual components/sources.

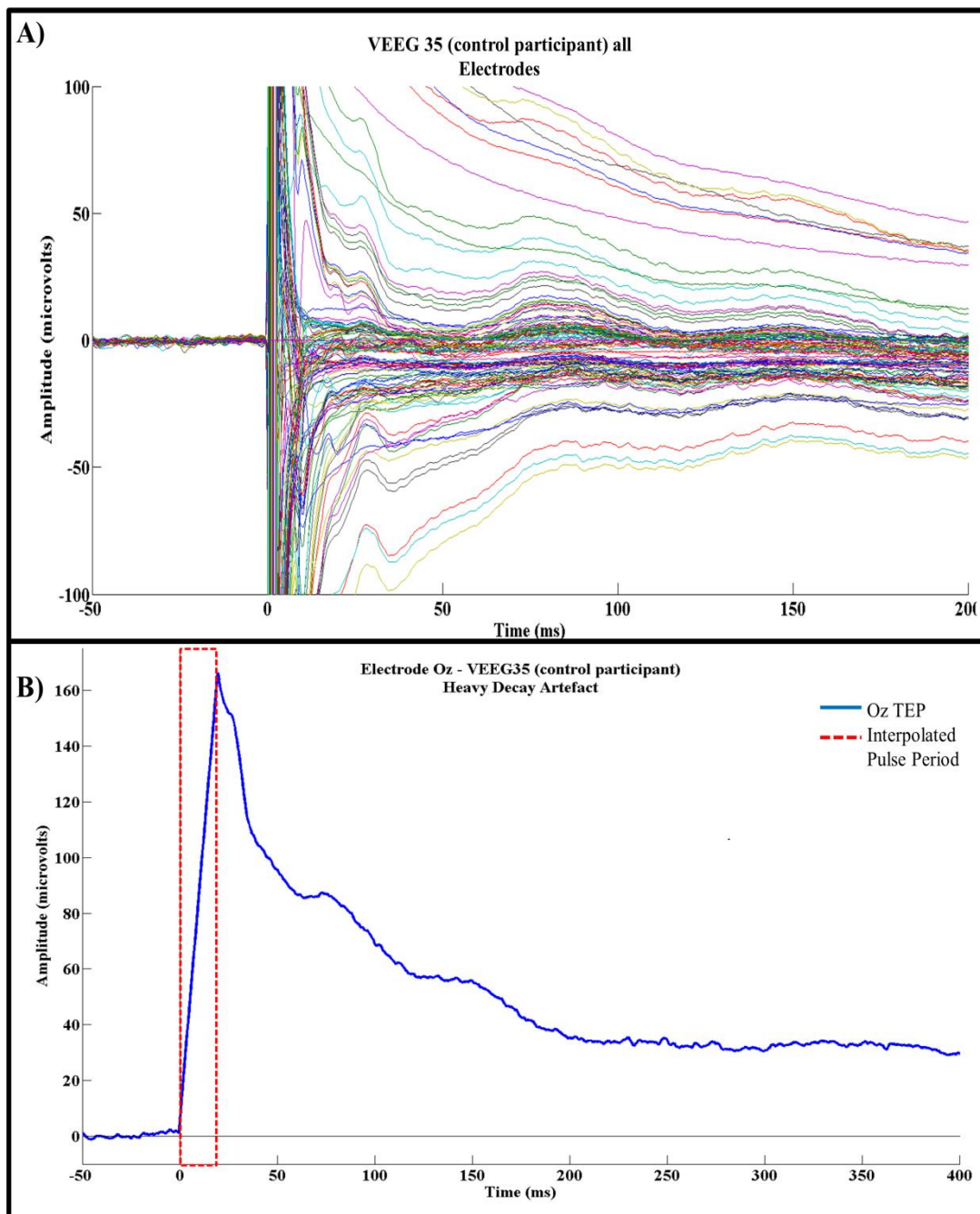


Figure 3.13, The effects of the transcranial magnetic current stimulation (TMS) pulse on concurrent electroencephalography (EEG) recordings in VEEG35 (control participant). A) Grand average of 240 trials at all electrodes with the pulse kept in to demonstrate the level of interference. B) Interpolation of the pulse period at electrode Oz.

Method for Stimulation Artefact Removal

The procedure for the removal of TMS artefacts is summarised in **Figure 3.14**. After identifying and removing bad channels the continuous data were segmented into epochs of 2048ms (stimulus \pm 1024ms), and the period immediately following the pulse (0-20ms) was replaced using linear interpolation (see **Figures 3.13 & 3.14**). Independent components were estimated with the FASTICA algorithm (Hyvärinen et al, 1999), using the tanh contrast function and symmetrical approach to decomposition to limit the likelihood of overfitting (Korhonen, 2010; Korhonen et al, 2011).

Independent components which predominantly characterised the slow-wave decay were identified by visual inspection (see **Figure 3.15**) and removed from the data if the majority of their spectral content was within the delta band (1-3 Hz). Spectral content was estimated using Welch's method of power spectral density (PSD; Welch, 1967; Mathworks, 2012). The power spectrum density (PSD) procedure works by performing the fast Fourier transform (FFT, Mathworks, 2012) within a window of a given period of time which is moved by x amount of samples until the end of the signal is reached. The spectral contents are then averaged across the windows to cancel out noise related fluctuations in the frequency power (Press et al, 1992). Components containing a mix of decay and cortical (TEP) activity were not removed. **Figure 3.15** demonstrates the effect of removing these components in data heavily contaminated by the decay artefact.

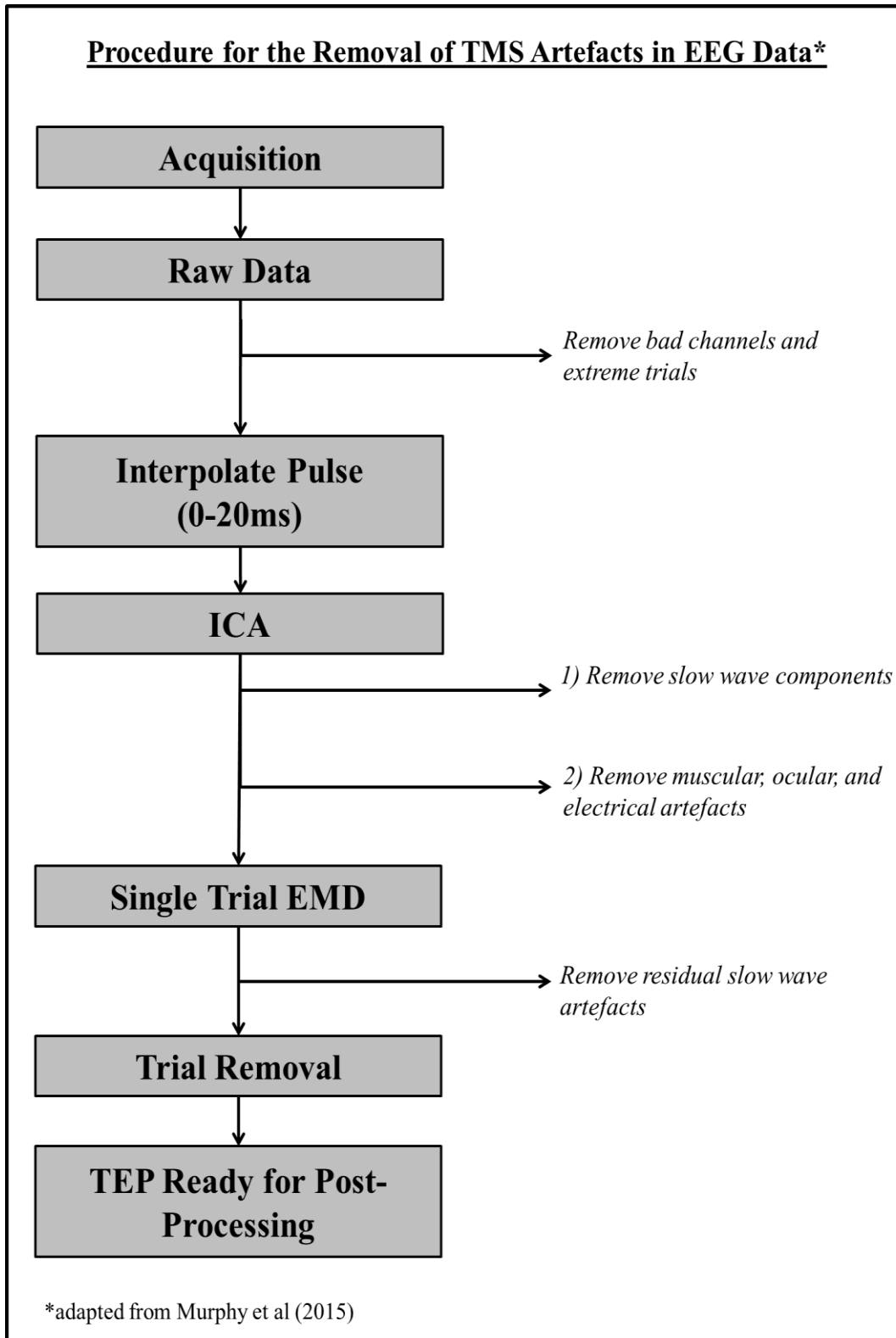


Figure 3.14, Schematic illustration of the transcranial magnetic stimulation (TMS) artefact removal paradigm. Abbreviations: ICA – independent components analysis; EMD – empirical mode decomposition.

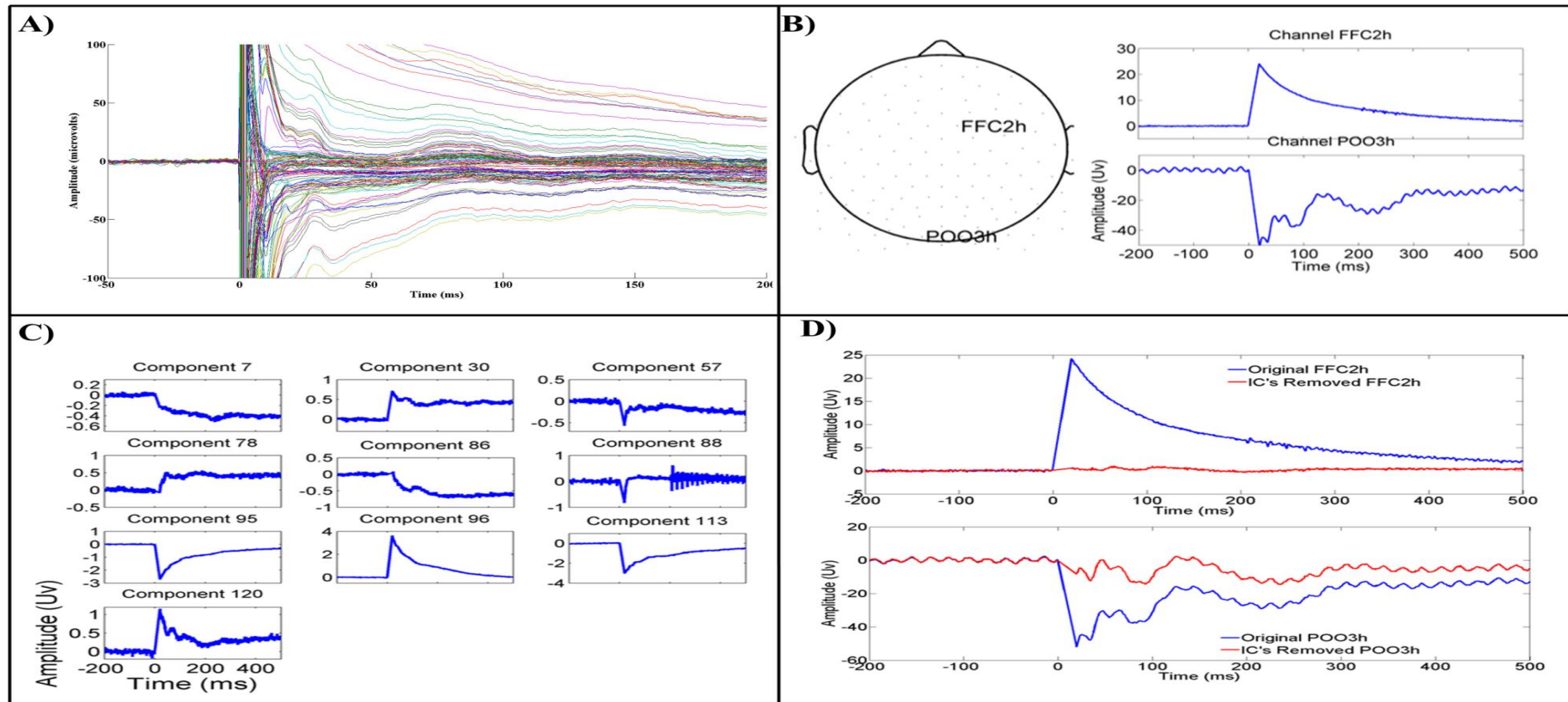


Figure 3.15, Demonstration of the process for removing the decay artefact. In (A) the data shown reflect the extent of the artefact in the unprocessed data. B) Electrodes FFC2h and POO3h are used as examples of affected channels; in POO3h the decay is mixed with an obvious transcranial magnetic current stimulation (TMS) evoked potential. C) Independent components analysis (ICA) decomposition reveals ten components that represent the slow wave/decay properties of the TMS artefact. When these are removed the potential of the data is greatly reduced and it is possible to measure the evoked potential. Importantly there is no difference between the component structures in the waveforms before and after ICA cleaning.

After removing the components contributing to the slow-wave magnetic artefact (decay) the pruned data were submitted to a second round of ICA to help identify muscular artefacts, as well as any possible ocular or electrical (50Hz) artefacts (see Jung et al, 2000). Despite being able to reduce the contributions of the TMS and related artefacts to the EEG recordings it was not always possible to perfectly separate the magnetic (decay) artefacts from cortical activity. The result of this was some residual slow-wave influences on the data, often causing changes in the baseline potential or linear trends (as seen in **Figure 3.16 B**) that remained for the duration of the epoch. Therefore in order to improve the validity of the TEP measurements the single trial data were baseline corrected using empirical mode decomposition (EMD, Huang et al, 1998). Empirical mode decomposition estimates n intrinsic mode functions (IMFs) by subtracting the mean of the temporal envelope from the original signal; the first IMF is then subtracted from the original signal and the procedure is repeated. The result is a series of functions representing different spectral characteristics of the data in time, with each IMF containing lower frequency content than the last (Huang et al, 1998). The concept of EMD makes it ideally suited to removing the remaining magnetic artefacts without distorting the data through the use of filters (spatial or otherwise). For each trial the spectral content of the IMFs was estimated using the FFT; IMF's representing purely delta range contributions (1 to 3Hz) were excluded when recombining the IMF's.

EMD is not widely used in EEG signal processing, although it is gathering strength as a simple tool to improve the clarity and reliability of clinical EEG recordings (Zhang et al, 2008), and therefore its use in the present study is experimental. However, there is an absence of a gold-standard procedure for TMS artefact removal and the EMD procedure provides good face validity particularly when considering between group comparisons. The procedures described above are, based on, and adapted from procedures applied in previous research, and highlight that there is still much future work required to hone this process.

After reducing the impact of the TMS artefacts, filtering was applied and the data were pre-processed. These steps are described in detail in **Chapter 6**.

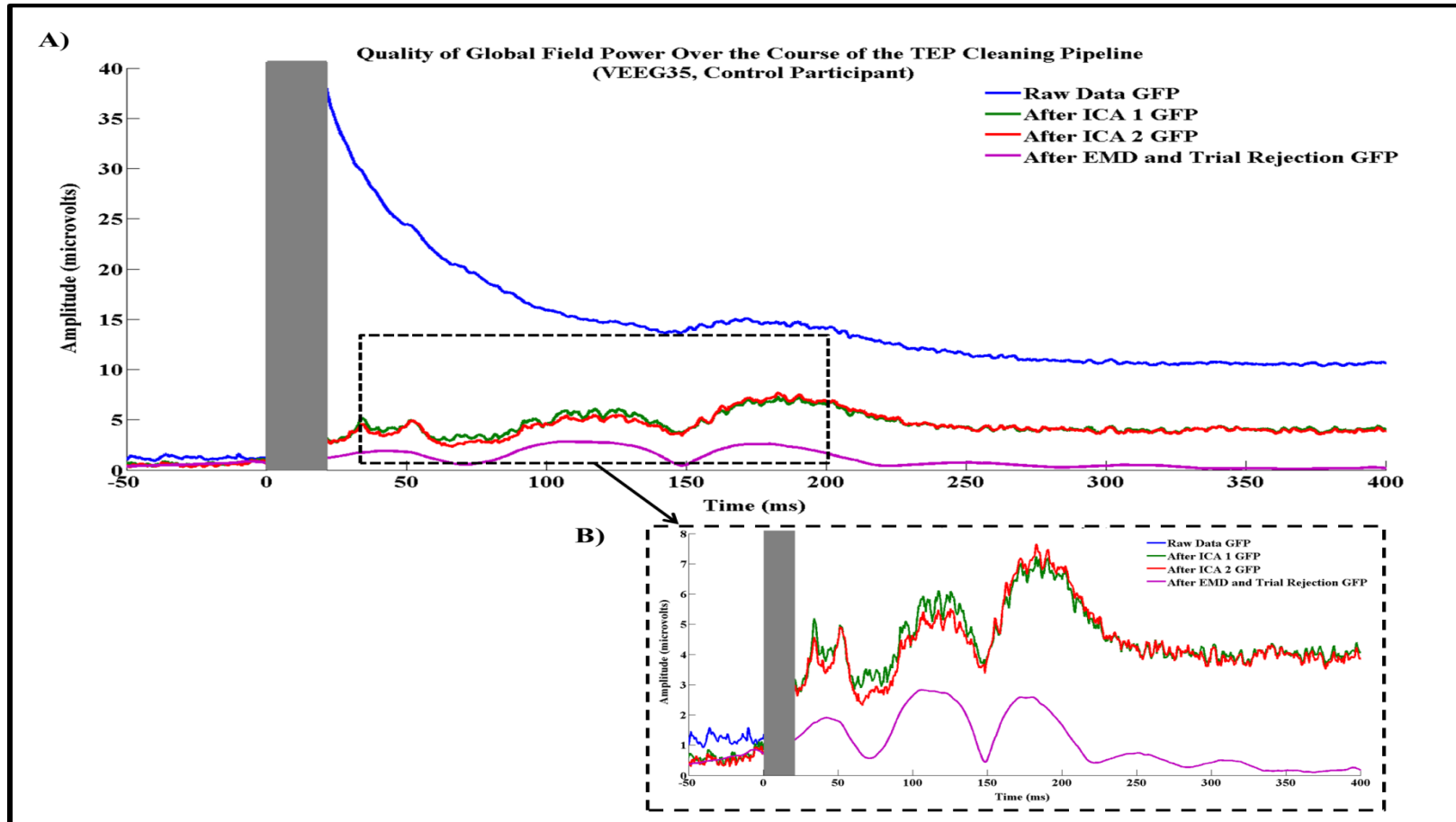


Figure 3.16, A demonstration of the reliability of the independent components analysis (ICA) approach for the removal of transcranial magnetic current stimulation (TMS) artefacts in electroencephalography (EEG) data (A & B – the scale is enlarged in B to better demonstrate the differences in the GFP in the later stages of the pipeline). This plot shows the global field power (GFP) for VEEG35 (control) after each stage in the cleaning pipeline. At each stage the influence of the slow-wave and other artefacts were reduced but without compromising the structure of the underlying evoked response.

Reliability of Stimulation Artefact Removal

As mentioned above the process of TMS artefact reduction using ICA is experimental and has not yet arrived at a consistent standardised approach. However, several recent articles have demonstrated that the artefact sources can be reliably estimated and removed from the data without distorting the pattern of the evoked response (Rogasch et al, 2014; Murphy et al, 2015). At each stage in the pre-processing of the TMS-EEG data the GFP was estimated to observe the extent of the artefact across the scalp, and to monitor changes in the pattern of the evoked response relative to the manipulations performed to reduce the artefact. In a subset of participants the data were subjected to analysis of test-retest reliability (see Murphy et al, 2015, listed in **Appendix 3**); multiple independent repetitions of the pre-processing steps (starting with raw data each time), demonstrated that the extent of the artefact in terms of the potential of the early portion of the post TMS signal was significantly reduced as an effect of the ICA procedure, but was not significantly different between independent repetitions. Each independent repetition removed similar numbers of and resulted in the GFP retaining the same number of peaks throughout. The outcome of these reliability assessments can be taken as preliminary evidence that ICA can be used reliably as an efficient tool for the reduction of TMS artefacts in EEG without compromising the quality of the signal taken to analysis (see **Figure 3.16**).

3.6 Statistical Analyses of Demographic and Electroencephalography Data

3.6.1 Normality

For all comparisons the data were inspected for violations of normality using the Shapiro-Wilk (SW) test due to it being more sensitive to small sample sizes than the Kolmogorov-Smirnov test (Shapiro et al, 1968; Howell, 2012). Significant violations were reported when the alpha value was less than 5% ($p < .05$). The outcome of the SW test was supported using visual inspection of the data's Q-Q plot and histogram. If the data did not demonstrate a significant SW value the group analyses were conducted using appropriate parametric tests, whereas non-normally distributed data were compared using non-parametric tests.

3.6.2 Covariates

In some cases the dependent variable may be influenced by other environmental variables/confounds such as age or medication. Covariates were identified by performing Spearman's correlations between the dependent variable and any variables that had previously

been documented as having an effect on the measurement of the dependent variable. Variables with significant ($p < .05$) correlations were entered into a stepwise regression analysis to test their ability to predict the dependent variable (linear regression was used for continuous variables; logistic regression was used for categorical variables). The regression analysis used backwards elimination of variables based on their likelihood ratio to identify significant predictors. When appropriate, significant predictors were controlled for in group comparisons so as to avoid misinterpreting the true effect of group membership on the dependent variable.

3.6.3 Reporting of Results

Group comparisons are summarised in the thesis as the mean measurement plus/minus (\pm) the standard deviation (e.g. $x (\pm y)$). Where appropriate figure/table legends use symbols to indicate different statistical tests. In tables significant p values are highlighted using a bold font.

Chapter 4 Demographics and Visual Symptoms

“There are more things in heaven and earth ... than are dreamt of in your philosophy.”

- Hamlet (1.5.167-8), (Shakespeare, W., 1603)

4.1 Introduction

Both Parkinson’s disease with dementia (PDD) and idiopathic Parkinson’s disease (PD) patients demonstrate deficits at a number of different levels in visual processing (Mosimann et al, 2004; Emre, 2007; Archibald et al, 2011;Urwyler et al, 2014). Some aspects of these have been associated with alpha-synuclein and Lewy body deposition in the dorsal (Mosimann et al, 2004; Pagonabarraga, et al, 2014), and ventral (Harding et al, 2002) streams, with PDD patients often performing worse on tests of mental rotation (Kerai, Bracewell et al, 2012), picture matching (Frank et al, 1996), as well as verbal and category fluency (Levy et al, 2002; Mahieux et al, 1998) compared to PD patients and controls. Additionally, the depletion of cholinergic neurons has been suggested to alter the vigilance of the primary visual cortex, affecting task performance when focussed attention is required (e.g. during visual search, Bosboom et al, 2009).

Of the documented visual symptoms, and complaints, visual hallucinations (VH) represent the most complicated and poorly understood symptom in PDD. Visual hallucinations can occur in PD prior to the development of a more severe cognitive impairment (Emre et al, 2007; Llebaria et al, 2010; Pagonabarraga et al, 2013; Pagonabarraga et al, 2014), although the role of cognitive impairment is clearly important (e.g. Llebaria et al, 2010; Shine et al, 2014; Peraza et al, 2014), with the visual system producing more phenomenologically complex hallucinations as the disease (and additional cognitive impairments) progresses (Goetz et al, 2008; Barnes et al, 2003; Llebaria et al, 2010). An array of studies have attempted to confront this challenge by investigating factors (and/or combinations of) that could act as predictors of visual hallucinations in both demented and non-demented PD, such as retinal dopamine deficiency (Nightingale et al, 1986; Archibald et al, 2009; Harnois & Di Paolo, 1990; Diederich et al, 2005), severity of motor symptoms (Rana et al, 2012); eye disease and related visual complaints (Archibald et al, 2011; Urwyler et al, 2014), cerebral hypoperfusion (Gasca-Salas et al, 2015), cognitive decline (Meppelink et al, 2009), sleep disturbances (Gama et al, 2015) and cortical atrophy (Sanchez-Casteneda et al, 2010).

The pitfall of much previous research has been the failure to address the experience of VH as belonging to a spectrum although the aetiological basis for different types of VH may be different (Archibald et al, 2011). For example, the so-called minor hallucinations of presence

and passage have been reported in much less developed cases of PD and in the absence of cognitive impairment (Pagonaboranagah, et al, 2014). However these minor VH have failed to show any predictive power for complex VH (Urwylar et al, 2014), suggesting that they may arise from alterations in the neural systems which are discrete to those involved in complex VH (Archibald et al, 2011).

This chapter describes the demographic and cognitive characteristics of the PDD group relative to the control group. Both groups were matched to minimise confounders, particularly age related changes in visual physiology that could skew the interpretation of results. The PDD patients were expected to demonstrate more visual impairments, and to deviate from the control group in terms of global cognitive ability. The secondary purpose of this chapter is to characterise the visual complaints in both groups and their association with visual hallucinations in the PDD group.

4.2 Methods

4.2.1 Participants

Twenty six PDD patients (mean age = 74.35 ± 5.8 , five female), and seventeen healthy controls (mean age = $75.47 \text{ years} \pm 5.4$, seven female), were consented and approached for baseline assessment. The process for recruitment and testing is described in **Chapter 3**. Due to fatigue not all participants were able to complete the battery of tests during the home visit. The number of participants from each group that completed a test is listed with the relevant test scores in **Table 4.2**.

4.2.2 Statistical Analyses

Between groups comparisons of demographic and neuropsychological scores were performed using independent samples t-tests, or Mann-Whitney's U for non-normally distributed data. The association between disease factors and cognitive scores were measured using Spearman's correlations, and corrected for multiple comparisons where appropriate. Data from the PDD group were tested for an effect of cholinesterase inhibitor use by comparing the scores of those on versus off medication using the Mann-Whitney U test.

The chi square test of independence was used to compare the frequencies of gender, and of visual complaints between groups. Visual complaints consisted of items taken from the North East Visual Hallucinations Index (NEVHI; **see Chapter 3**) that did not refer to visual hallucinations.

The overall experience of visual hallucinations was defined in terms of the severity of the experience (e.g. frequency, duration, content, and general disturbances), and rated by both the carers (NPI hallucinations subscale, **see Chapter 3**) and the patients. Patient ratings of experience were derived from their reports of frequency and duration in the NEVHI battery, and reflect the product of these two items. The output from this approach is comparable to the NPI hallucinations subscale score (i.e. frequency x severity of the hallucinations). However, NPI subscales have a maximum score of twelve (0-3 frequency; 0-4 severity), whereas the derived NEVHI has a maximum of nine (0-3 frequency; 0-3 duration). To directly compare the fit of the two ratings an alternate version of the NEVHI score was created (see **Equation 4.1**) whereby the total score was mapped onto the NPI hallucinations subscale score using the formula:

$$Y = \left(\frac{\max NPI}{\max NEVHI} \right) * NEVHI$$

Equation 4.1, The mapped NEVHI (Y) rating for direct comparison with the NPI rating of VH experience was created by dividing the two maximum possible scores, and then multiplying each individual score on the NEVHI measure by this value.

Disparities between mean group reports were tested using the Wilcoxon signed ranks test. Spearman's rho was used to identify the strength of the relationship between the two measures.

To investigate the association between visual complaints and the presence ("yes" or "no") of both simple VH (separate dependent variables for: *simple VH (e.g. lines, basic shapes); feelings of presence; shadow; objects appearing/disappearing; illusions; feelings of eyes playing tricks*), and complex VH a preliminary stepwise logistic regression analysis was performed. Visual complaints that were present in more than 30% of the PDD group were entered as independent variables to logistic regression models, performing correlation as an initial step, and backwards elimination of variables based on their likelihood ratio. Significance was reached at an alpha value with a probability of $p < .05$ (two-tailed) and supported by the width of the 95% confidence interval.

4.3 Results

A summary of the demographic information is shown in **Table 4.1**, and neuropsychological characteristics are described in **Table 4.2**.

4.3.1 Demographic Data

Both groups were matched for age ($t(41) = .636, p = .528, d = 0.19$), and as expected the PDD group demonstrated a significant global cognitive impairment relative to the control group (MMSE, $t(32.74) = .698, p < .001, d = 1.98$; CAMCOG total, $t(34.2) = 7.23, p < .001, d = 2.1$). The majority of PDD participants ($n = 14$) reported an onset of cognitive symptoms over two years ago, whereas $n = 7$ reported an onset within the last two years, and $n = 1$ participant was unsure of when cognitive symptoms had begun. A total of $n = 3$ PDD participants did not report having experienced the onset of any cognitive problems. The PDD group also displayed greater impairments on measures of memory (CAMCOG Memory subscale, $t(32.42) = 6.8, p < .001, d = 1.91$), and executive function (CAMCOG Executive subscale, $t(41) = 9.2, p < .001, d = 2.94$). Visual acuity was also reduced in the PDD group relative to the control group ($t(36) = 2.56, p = .015, d = 0.79$). The balance between male and female participants (male > female) was more disproportionate in the PDD group than the control group. However, this difference was not significant ($\chi^2 = 2.46, DF = 1, p = .168, CV = .24$). Nineteen out of 26 PDD patients had complex recurrent visual hallucinations with a mean NPI hallucinations subscale score of 2.36 (± 2.66 ; minimum = 1, maximum = 8). The extent of VH severity did not influence the PDD global cognitive scores (see **Table 4.3**).

4.3.2 Motor and Medication Factors

The average duration of motor symptoms was 9.1 years (± 6.6). Twenty-five (96.2%) out of 26 patients were taking PD medications (mean = 1.96, ± 1.1), of these 25 (96.2%) patients were taking levodopa (average dose = 716.92 mg, ± 392.04 mg). A total of $n = 10$ (38.46%) PDD participants were only taking levodopa for the treatment of Parkinsonism. Of the 25 PDD participants taking PD medications additional to levodopa $n = 6$ were taking two medications (including levodopa), $n = 7$ were taking three medications (including levodopa), and $n = 2$ were taking 4 medications (including levodopa). As there is a history of reports concerning the exacerbation of VH by dopamine agonists (Diederich et al, 2004; Banerjee et al, 1989) the number of PD medications was tested for a relationship with carer and patient ratings of VH experience (overall severity). The number of PD medications was not related to carer ($r_s = .005, p = .98$) or patient ($r_s = -.008, p = .97$) ratings of VH experience.

PDD patients as expected had higher total UPDRS scores than did controls ($t(26.4) = -13.8$, $p < .001$, $d = -3.84$). Equivalent dosage of levodopa was unrelated to UPDRS total measurement ($r_s = -.021$, $p = .92$), and other demographic factors when corrected for multiple comparisons ($\alpha = .012$, all $p > .05$). A trending relationship was observed between equivalent levodopa dosage and performance on the CAMCOG memory battery ($r_s = .48$, $p = .014$). Approximately half of PDD participants were on treatment doses of cholinesterase inhibitors (46.2%), and two PDD participants were taking memantine.

4.3.3 Neuropsychological Data

Cognitive Fluctuations

Fluctuations in confusion and level of consciousness were common in the PDD group (CAF score; $n = 23$ [88.46%] score > 0 ; mean 5.43 ± 3.8), with severe fluctuations (> 5) reported in $n = 13$ participants (50%, mean 8.15 ± 2.4). Severe fluctuations did not show a significant relationship with measures of cognitive impairment (CAMCOG total, MMSE, visual hallucination severity, verbal fluency, category fluency, trail making) when corrected for multiple comparison ($\alpha = .007$), instead only demonstrating a trending relationship with MMSE ($r_s = -.67$, $p = .011$). Across the whole PDD group fluctuations were less severe in those not taking cholinesterase inhibitors ($n = 11$, mean $= 3.73 \pm 3.95$) than those prescribed cholinesterase inhibitors ($n = 12$, mean $= 7 \pm 3.01$; $MWU = 31.5$, $Z = -2.15$, $p = .032$). However, in those with severe fluctuations, cholinesterase inhibitor use did not appear to influence mean fluctuation scores ($MWU = 16$, $Z = -.35$, $p = .83$).

Visual Perception

Participants in the control group performed better on tests of angle discrimination than PDD patients ($MWU = 26$, $Z = -4.22$, $p < .001$), and could more easily discern between the motion speeds of two objects ($MWU = 10$, $Z = -4.73$, $p < .001$). Control participants were more likely to report correct responses on the pareidolia task ($MWU = 34$, $Z = -3.84$, $p < .001$), and had less frequent reports of pareidolic images ($MWU = 46$, $Z = -3.6$, $p < .001$). PDD group performance on tests of visual perception was not related to the severity of visual hallucinations (see **Table 4.3**).

Visual Executive Function

Participants in the PDD group required significantly longer periods of time to complete part A of the trail making test, than did controls ($t(17.3) = -4.03$, $p < .001$, $d = -1.34$). Part B of the trail making test was only completed in four of the PDD group ($\chi^2 = 26.75$, $CV = .82$, p

<.001). Conversely, Mann-Whitney U comparison of those who completed the task did not show a significant difference in the median completion times between the groups ($U = 16$, $Z = -1.512$, $p = .148$). However, due to the small, and unequal, sample this should be interpreted with caution.

Verbal and Semantic Ability

PDD patients generated less words on the verbal fluency task (*PDD* mean = 17.46 ± 13.5 ; *Controls* mean = 47.1 ± 11.2 ; $t(39) = 7.41$, $p < .001$, $d = 2.38$) and the category fluency task (*PDD* mean = 9.63 ± 5.4 ; *Controls* mean = 17.53 ± 5.02 ; $t(40) = 4.9$, $p < .001$, $d = 1.55$), than the control group.

Table 4.2, Mean demographic factors per group and between group comparisons. Variations in statistical tests are denoted using the markings listed in the table legend.

Characteristic	Control (±)	PDD (±)	P Value	Effect Size	Confidence Interval (95%)	
					Lower	Upper
<i>Age</i>	75.47 (5.4)	74.35 (5.84)	0.53§	0.19 §	-2.5	4.7
<i>M:F (% Male)</i>	10:7 (58.8)	21:5 (80.7)	0.17†	0.24 †		
<i>Visual Acuity</i>	0.55 (0.32)	0.34 (0.2)	0.015 §	0.79 §	0.05	0.39
<i>UPDRS Total</i>	2.29 (2.7)	56.65 (19.8)	<.001§	-3.84 §	-62.5	-46.3
<i>CAMCOG Executive</i>	22.47 (2.9)	12.38 (3.9)	<.001 §	2.94§	7.9	12.3
<i>CAMCOG Memory</i>	23.53 (1.59)	16.54 (4.9)	<.001§	1.91§	4.9	9.1
<i>CAMCOG Total</i>	95.76 (6.3)	69.38 (16.92)	<.001 §	2.1 §	18.97	33.8
<i>MMSE</i>	29.24 (1.72)	21.62 (5.14)	<.001§	1.98 §	5.4	9.8

§ Independent samples T-test; Cohen's D; † Pearson's Chi Square test, Cramer's V

Table 4.3, Neuropsychological characteristics and between groups comparisons. Variations in statistical tests are denoted using the markings listed in the table legend.

	Controls		PDD		P Value	Effect size	Confidence Interval (95%)	
	n	mean (\pm)	n	mean (\pm)			lower	upper
<i>Angle Discrimination</i>	15	13.5 (19.3)	21	39.1 (28.4)	<.001 †	-0.70	-41.19	-10.01
<i>Motion Discrimination</i>	15	-2.4 (1.9)	21	3.16 (2.56)	<.001 †	-0.79	-7.02	-4.10
<i>Pareidolia (Correct)</i>	13	39.08 (1.12)	23	31.48 (5.53)	<.001 †	-0.64	5.26	9.94
<i>Pareidolia (Miss)</i>	13	0.23 (0.43)	23	2.7 (2.32)	<.001 †	-0.60	-7.20	-3.08
<i>Pareidolia (Pareidolic Images)</i>	13	0.69 (1.11)	23	5.83 (4.83)	<.001 †	-0.59	-3.45	-1.49
<i>Trail Making A (seconds)</i>	16	32.11 (9.6)	18	135.21 (108.1)	<.001 §	-1.34	-156.90	-49.20
<i>Trail Making B (seconds)</i>	16	63.58 (35.82)	4	149.68 (104.9)	0.15 †	4.47		
<i>Verbal Fluency</i>	17	47.1 (11.2)	24	17.46 (13.5)	<.001 §	2.38	21.52	37.48
<i>Category Fluency</i>	17	17.53 (5.02)	25	9.48 (5.36)	<.001 §	1.55	4.73	11.37
<i>NPI Hallucinations (frequency*severity)</i>		Not collected	25	2.36 (2.66)				
<i>NEVHI (duration*severity)</i>		Not collected	25	1.8 (1.73)				

§ Independent samples T-test (Cohen's D); † Mann-Whitney's U (*r*)

Table 4.4, Comparison of the associations between test items and visual hallucination severity reports.

Test Item	NPI Hallucinations		NEVHI	
	<i>rs</i>	<i>p</i>	<i>rs</i>	<i>p</i>
<i>MMSE Score</i>	-0.23	0.27	-0.17	0.41
<i>CAMCOG Executive</i>	-0.36	0.07	-0.24	0.25
<i>CAMCOG Memory</i>	-0.28	0.18	-0.22	0.29
<i>CAMCOG Total</i>	-0.34	0.10	-0.27	0.19
<i>Angle Discrimination</i>	0.02	0.94	0.01	0.95
<i>Motion Discrimination</i>	-0.06	0.80	-0.12	0.59
<i>Number of Pareidolic Images</i>	0.27	0.22	0.16	0.48
<i>Trail Making (part A)</i>	0.37	0.13	0.33	0.19

rs= Spearman's Rho;

4.3.4 Visual Complaints and Hallucinations

Visual complaints were reported almost exclusively in the PDD group (see **Table 4.7**). The exceptions to this were blurred vision (Controls, $n = 3$; PDD $n = 6$), and double vision (Controls $n = 1$, PDD $n = 15$). Chi squared results revealed that blurred vision was likely a chance occurrence within each sample and not dictated by group membership ($\chi^2 = .18, p = .72, CV = .06$). Double vision was seen in 57.7% of PDD patients compared to 5.9% of control participants.

Simple VH were reported exclusively in the PDD group, except for presence hallucinations which were reported in one control. Free text commentary on this NEVHI item revealed that presence hallucinations in this individual were only experienced whilst practicing reiki. In the PDD group the most commonly reported simple VH were the feelings of eyes playing tricks (76.92%) and presence hallucinations (61.64%). The remaining variants of simple VH were consistently reported in fewer than 50% of the PDD group. Complex VH were an exclusive feature of the PDD group and reported in 69.2% of cases.

The extrapolated measure of patient reported VH experience (NEVHI patient version) was positively correlated with the carer report of VH experience (NPI hallucinations subscale frequency*severity) from the NPI subscale for hallucinations ($r_s = .852, p < .001$). A total of six cases showed a discrepancy of more than half of a standard deviation in their scores.

Table 4.5, Comparison of frequencies for visual complaints and hallucinations between groups.

	Count (%)		$\chi^2(p)$	Cramers V
	Controls (\pm)	PDD (\pm)		
Visual Complaints				
Blurred Vision	3 (17.7)	6 (23.1)	.18 (.72)	0.06
Double Vision	1 (5.9)	15 (57.7)	11.81 (.001)	0.52
Dry/Painful Eyes	0 (0)	9 (34.6)	7.44 (.007)	0.42
Light Sensitivity	0 (0)	5 (19.23)	3.7 (.14)	0.29
Misjudging Objects	0 (0)	10 (38.5)	8.52 (.007)	0.44
Freeze Whilst Walking	0 (0)	9 (34.62)	7.44 (.007)	0.42
Moving Words	0 (0)	6 (23.1)	4.56 (.06)	0.33
Visual Hallucinations				
Eyes Playing Tricks	0 (0)	20 (76.92)	24.45 (<.001)	0.75
Presence	1 (16.67)	16 (61.54)	13.32 (<.001)	0.56
Shadows	0 (0)	9 (34.6)	7.44 (.007)	0.42
Illusions	0 (0)	8 (30.8)	6.43 (.014)	0.39
Objects Appearing/Disappearing	0 (0)	11 (42.3)	9.66 (.003)	0.47
Lights	0 (0)	3 (11.5)	2.11 (.27)	0.22
Simple (Geometric)	0 (0)	7 (26.9)	5.47 (.031)	0.36
Complex	0 (0)	18 (69.2)	20.24 (<.001)	0.69

4.3.5 The Relationship between Visual Complaints and Visual Hallucinations

Double vision (DV), dry/painful eyes (DP), misjudging objects (MO), and freezing whilst walking (FWW), were reported in more than a third of PDD patients (see **Table 4.7**) and tested for a relationship with the presence visual hallucinations. The misjudging of objects, but not the other visual complaints, was associated with the occurrence of presence hallucinations ($\beta = 2.41$, $se = 1.1$, $p = .029$). However, the confidence interval was wide on this relationship (1.3 to 97.03) and thus needs to be interpreted cautiously. None of the visual complaints were associated with the presence of complex VH (all $p < .05$). None of the simple VH variables showed a significant relationship with complex VH (all $p < .05$).

4.4 Discussion

The PDD and control groups were both well matched for age, and showed no comorbid features that might interfere with accurate interpretation of results. Both groups contained more male participants than females and this is consistent with prior evidences supporting a male preponderance in PDD (Wooten et al, 2004; Gillies et al, 2014).

In PDD cholinergic and dopaminergic neurons are greatly depleted (Caballol et al, 2007; Pillon et al, 2003; Perry et al, 1983; Bosboom et al, 2004; Perry et al, 1985; Hitehouse et al, 1983), in lieu of the widespread cortical damage seen in other forms of neurodegenerative dementia. These impairments and neurotransmitter disturbances have been linked to disruptions in the regulation of attention across multiple domains, although executive (Mattila et al, 2000; Perry et al, 1983; Perry et al, 1985) and visual (Stoffers et al, 2007; Bullock et al, 2002; Ziabreva et al, 2006; Ferman et al, 2013) systems appear to be disproportionately affected. In the present study the pattern of cognitive impairment seen in the PDD group was consistent with previously documented accounts (e.g. Caballol et al, 2007; Emre et al, 2007), with PDD showing increased global cognitive impairment, including decline on tests of memory and executive function.

Fluctuations in consciousness and cognition were present in the majority of PDD participants, and demonstrated a trend towards increasing severity alongside greater global cognitive impairment, but not with decline in specific cognitive sub-domains. As expected as the severity of cognitive symptoms increased patients were more likely to be on psychotropic medication. However, increasing motor symptom severity was not associated with an increased equivalent levodopa dosage. Likewise the equivalent dosage did not show any relationship with the severity of visual hallucinations, or global cognitive function, except for the CAMCOG memory task, in which scores were increased with more intensive levodopa

therapy. This could be due to the promotion of improved dopaminergic signalling between the midbrain and the hippocampus leading to enhanced long term potentiation (Wittmann et al, 2005).

4.4.1 Visual Symptoms

Evaluation of the visual symptoms and complaints in the PDD group was consistent with previous reports (e.g. Mosimann et al, 2004; Urwyler et al, 2014), showing marked impairment of visual perceptual and visual attention functioning, as well as deterioration of visual acuity. The latter finding suggests that PDD pathology extends beyond the visual and visual associative cortices, but is also disrupting elements of the transmission of visual input to the primary visual cortex (Nightingale et al, 1986; Archibald, 2009).

There is a building consensus that the underlying aetiology of VH is likely to be multifaceted (Collerton et al, 2005; Shine et al, 2011; ffytche et al, 2008). However, confusion remains when trying to determine which combination of factors are important in the generation of VH in PDD. A mixture of neuroimaging (e.g. Shine et al, 2014; Peraza et al, 2014), cognitive modelling (e.g. Collerton, et al, 2005; Diederich et al, 2004; Tsukada et al, 2014), and neuropsychological test findings (Barnes, 2015; Barnes & Boubert, 2008) have led to the suggestion that VH arise from poor handling of an already degraded visual input, with the poor input acting to overburden an already constrained system which results in the perceptual information being bound to an incorrect template (Collerton et al, 2005; Boubert & Barnes, 2015). This is elegantly reflected in the findings from the pareidolia task in the present study, where PDD patients were more likely to misinterpret random noise as salient features of an image. This finding has also previously been demonstrated by Yokoi and colleagues (Yokoi et al, 2014) who observed that pareidolia were more frequently reported in PD with VH and dementia with Lewy bodies, than PD without VH and controls. Although this was not an exclusive feature of pathology associated with VH Yokoi et al interpreted this as being linked with posterior cortical disruption and cholinergic depletion (Yokoi et al, 2014). A follow-up study using positron emission tomography (PET) confirmed that the frequency of pareidolia was correlated with reduced metabolism in the temporal, parietal, and occipital cortices, and further related to reduced MMSE score (Uchiyama et al, 2015) implying widespread disruption to the visual system and global cognitive function may be a necessary pre-requisite for the manifestation of VH, at least in Lewy body disease.

A lack of association between complex and simple VH was observed in the present study. This is consistent with two recent studies which tested associative/predictive factors for

complex and simple VH (Urwyler et al, 2014; Archibald et al, 2011). Archibald and colleagues found that simple VH (presence, and illusions) had different clinical predictors to complex VH, with the former being predicted by Parkinson's severity (UPDRS III) and sleep disturbances. This was in comparison to the predictors for complex VH which were dementia severity, mood disturbances and visual acuity. Urwyler et al sought to identify the likelihood of visual complaints as predictors of simple and complex VH (whilst controlling for cognitive impairment). This revealed that presence and passage hallucinations were predicted by double vision, and the misjudging of objects. Conversely, complex hallucinations could not be predicted by complaints. In the present study a similar pattern of associative factors was observed to the Urwyler et al study, and also failed to predict complex VH using visual complaints. Based on a lack of association this supports the argument made by Archibald et al. that despite being common in PDD simple and complex VH may have different neural substrates.

4.4.2 Measurements of Visual Hallucination Experience

In many previous studies the NPI subscale for hallucinations has been used to measure the severity and frequency of VH. This is likely due to its widespread use in clinical trials, simple structure, and mainstream accessibility. The drawback is that this measures hallucinations according to the care-giver, and is therefore an indirect and subjective measure. Conversely, when patients are interviewed it is not uncommon for them to initially fail to disclose a full account of their experiences with VH (Gupta et al, 2004; Williams et al, 2008). It is therefore not beyond the realms of possibility that a patient may feel obliged to withdraw a full account of their experiences from a spouse or relative to help reduce distress, or feel there is a stigma associated with disclosure of these perceptual experiences. Whilst these are less likely to be factors in patients with cognitive impairment (in contrast to those with, for example, eye disease), memory deficits and recall of hallucinatory events may be disturbed leading to under-recognition or reporting of events to care-givers and clinicians.

There is no ideal scale by which to measure these subjective phenomena. However, the combination of both a patient (NEVHI) and carer (NPI hallucinations subscale) rating allowed improved reliability. Certainly in the present study after mapping the NEVHI scores to the NPI hallucinations subscale score scale it emerged that both measures in the same patient reported similar levels of VH severity. The importance of this is that the data accurately reflect the experience of the hallucinations, allowing for further comparisons between electrophysiological measures and VH severity without making invalid conclusions.

A final point is that non-hallucinating PDD patients are often used as a comparison group to examine the aetiology in PDD. However, it was relatively difficult to recruit non-hallucinating PDD patients as frequently those reported as non-hallucinators in clinical records, on careful questioning during the research assessments, evidenced a history of VH in the present study. Although this is not favourable, it does not negatively impact the additional analyses described in this thesis as a dimensional approach can be taken i.e. correlate the spectrum of VH frequency/severity with neurophysiological measures. Conversely, this does limit the scope for drawing conclusion from the dataset as the effect of hallucination will be examined as part of a scale rather than as a dichotomy. Nevertheless, several experts in the area have argued that such splits may be artificial as the difference between hallucinators and non-hallucinators may be that in the latter, the threshold at which these phenomena are experienced has not been breached but that this does not mean these individuals do not have some of the features of a hallucination-prone visual system (Llebaria et al, 2010; Murphy et al, 2015; Pagonabarraga et al, 2015). Thus taking a dimensional approach which considers frequency and severity may be more appropriate.

Chapter 5 Markers of Early Bottom-Up Visual Information Processing in Parkinson's Disease with Dementia Patients: A visual evoked potential study

“We can easily forgive a child who is afraid of the dark; the real tragedy of life is when men are afraid of the light.” – Plato, Remarks of Famous People

5.1 Introduction

Even prior to the onset of dementia Parkinson's (PD) patients will often display a number of visual complaints (Naylor, 2005; Archibald, 2009) including, for example, poor contrast sensitivity (Price et al, 1992; Lin et al, 2015; Bulens et al, 1986), poor visual acuity (Holroyd et al, 2001), and reduced sensitivity to motion (Mosimann et al, 2004). Deficits, such as these, occurring in the bottom-up stream of processing appear to play a central role in deafferentation models of visual hallucinations (VH; Manford & Andermann, 1998; Burke, 2002) and in particular the syndrome of Charles Bonnet, which is associated with macular degeneration (Abbot et al, 2007; ffytche, 2005). Visual hallucinations in non-demented PD are reported in fewer than 50% of cases (45%, Aarsland et al, 1999; Fenelon et al, 2000), yet act as reliable predictors of cognitive decline (Aarsland et al, 2003), and are prevalent in up to 65% of PDD cases (McKeith et al, 2005). Differences in VH phenomenology between patients at varying stages of cognitive impairment (Onofrj et al, 2007; Fenelon, 2008; Llebaria et al, 2010) suggests that multiple dysfunctions in visual processing might be implicated in the genesis of VH.

Despite the growing pool of knowledge surrounding the higher cognitive correlates of VH little is understood about the precise contributions of bottom-up visual input towards the experience of VH in PDD. Recent neuropathology suggests that the transfer of visual information from the retina to the visual cortex remains intact in Lewy body dementia (LBD) with VH (Erskine et al, 2015). However, this is in contrast to historical accounts of retinal information transfer which suggest that this process is abnormal in patients with PD (Bodis-Wollner, 1978) as quantified using pattern reversal visual evoked potential (VEP). In clinical use the P1 (also referred to as the P100) component of the VEP has been used as a marker of conduction velocity, typically showing an increased latency in patients with PD (Bodis-Wollner, 1978; Calzetti et al, 1990).

The lack of consensus relating to the role of low level visual deficits in the occurrence of VH in PDD implies that this symptom is subserved by more complex processes. Indeed in the context of modern models of VH (e.g. Diederich et al, 2004; Collerton et al, 2005; Shine et al, 2012; Shine et al, 2014) it is likely that the process of dysfunctional visuo-attentional binding, a feature common to PDD (Sanchez-Castaneda et al, 2010; Collerton et al, 2005), would contribute synergistically with declining visual function in predisposing individuals to VH.

In this chapter the aim was to characterise the neurophysiological components of early bottom-up processing in PDD using the VEP, and to relate the response features to VH severity (the measure of VH experience using the NPI hallucinations subscale and/or NEVHI measures described in **Chapters 3 & 4**). This study begins by exploring the potential impact of demographic factors on the VEP, and then compares and contrasts the three main components in the VEP waveforms (N1, P1, & N2) between PDD and aged controls. Finally this chapter examines the relationship between VEP component measurements and reports of the severity of the VH experience (see above).

5.2 Methods

5.2.1 Participants

Pattern reversal VEPs were recorded from $n = 17$ healthy controls (mean age = 75.47 years, ± 5.4) and $n = 22$ Parkinson's disease with dementia (PDD) patients (mean age = 73.43 years, ± 5.7). Two PDD patients were excluded from analysis due to a history of eye disease, and P1 component latencies greater than three standard deviations from the group mean. A further PDD patient was excluded due to an occipital structural abnormality detected on their structural MRI which may have made the appropriate placement of the electrode montage unreliable. Thus the final VEP analyses were conducted using $n = 17$ healthy controls and $n = 19$ PDD patients (mean age = 72.74, ± 5.4).

5.2.2 Data Acquisition

The display parameters for the VEP stimulus are described in detail in **Chapter 3**. The stimulus was presented for two blocks of fifty seconds (100 reversals in each) separated by a rest period of two seconds (see **Figure 5.1**). During the rest period the display would turn grey whilst retaining the focus point to reduce wandering gaze. Three separate recordings were taken from each participant: viewing with both eyes; viewing with left eye; viewing with right eye. The three recordings were used to help screen for inter-ocular variations that could have indicated undocumented eye disease.

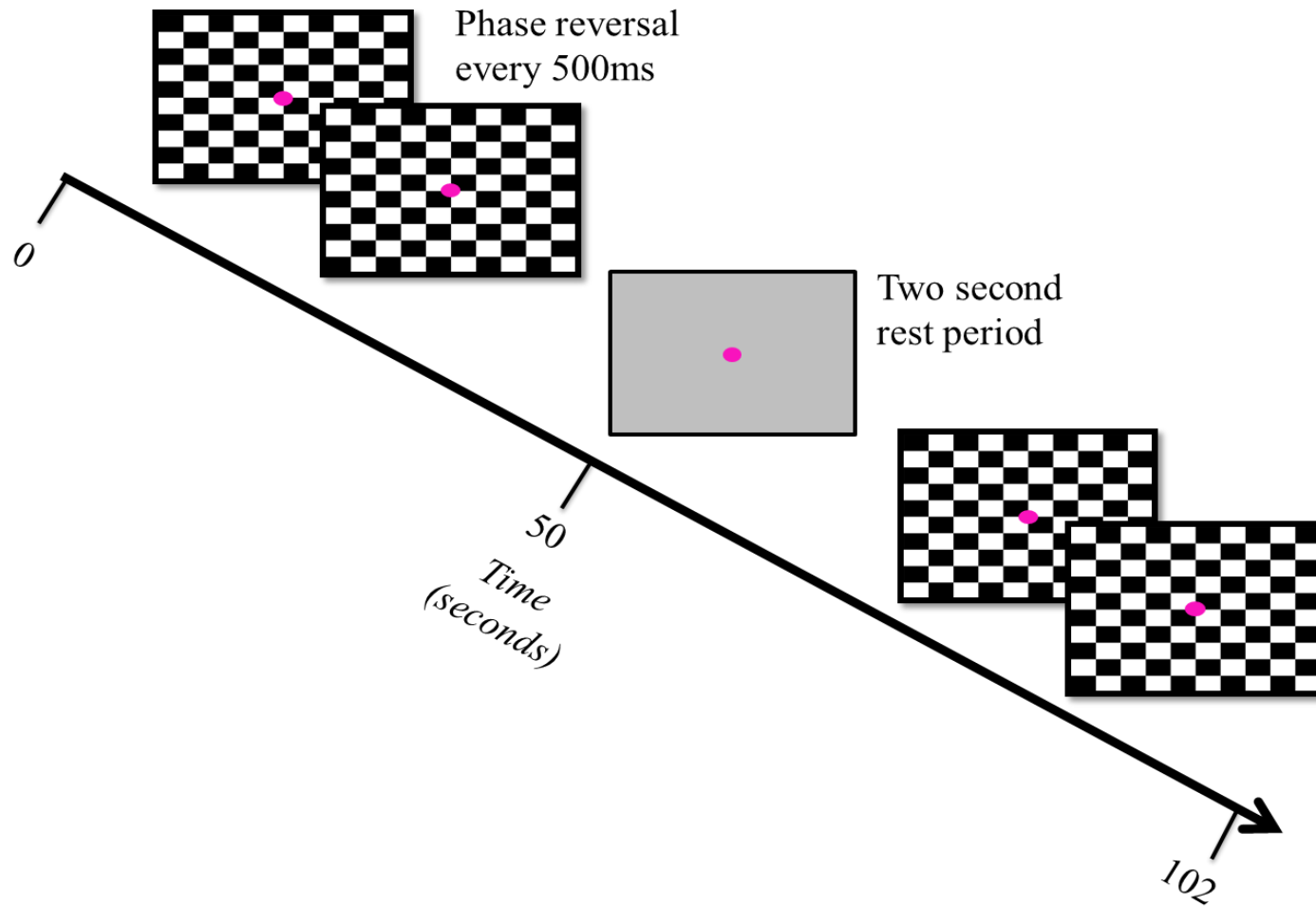


Figure 5.1, Temporal schematic demonstrating the process of stimuli presentation during the visual evoked potential task. The focus point was displayed as a pink dot throughout the stimulus.

5.2.3 *Data Analysis*

For formal assessment of the VEP it is usual to apply a window of 200ms. However, the latencies of the VEP components have previously been shown to be affected by both age and PD (Bodis-Wolner & Yahr, 1978; Sokol et al, 1981; Nightingale et al, 1986). To account for possible changes in component latency single trial VEPs were windowed using an epoch of 400ms (300ms post-stimulus, 100ms pre-stimulus). Although it is recommended to use a pre-stimulus baseline period of approximately 200ms for event related potentials (e.g. Luck, 2005, ch4.) due to the quick succession of trials in the VEP paradigm a shorter baseline was utilised to prevent the introduction of activity from the end of the previous trial in the baseline of the current trial. Single trials were baseline corrected using the mean of the data in the pre-stimulus period of the epoch and filtered using a 0.1 to 45Hz bandpass filter. Bad channels and trials were identified and removed using the principals described in **Chapter 3**.

Due to the problem with the mixing of sources in EEG the electrodes chosen to represent the primary visual cortex were kept to a minimum. A region of interest was created using the electrodes O1, Oz, & O2 (see **Figure 5.2**) and the signals from these electrodes were averaged to improve the resolution of the VEP. In the 10-5 montage (Oostenveld & Praamstra, 2001) these electrodes are located roughly equivalent to the underlying Brodmann area 17. The measurement windows for the VEP were defined using the global field power maxima (peak +/- 20ms). Component peak latency and peak amplitude measurements were taken from the region of interest average within these windows.

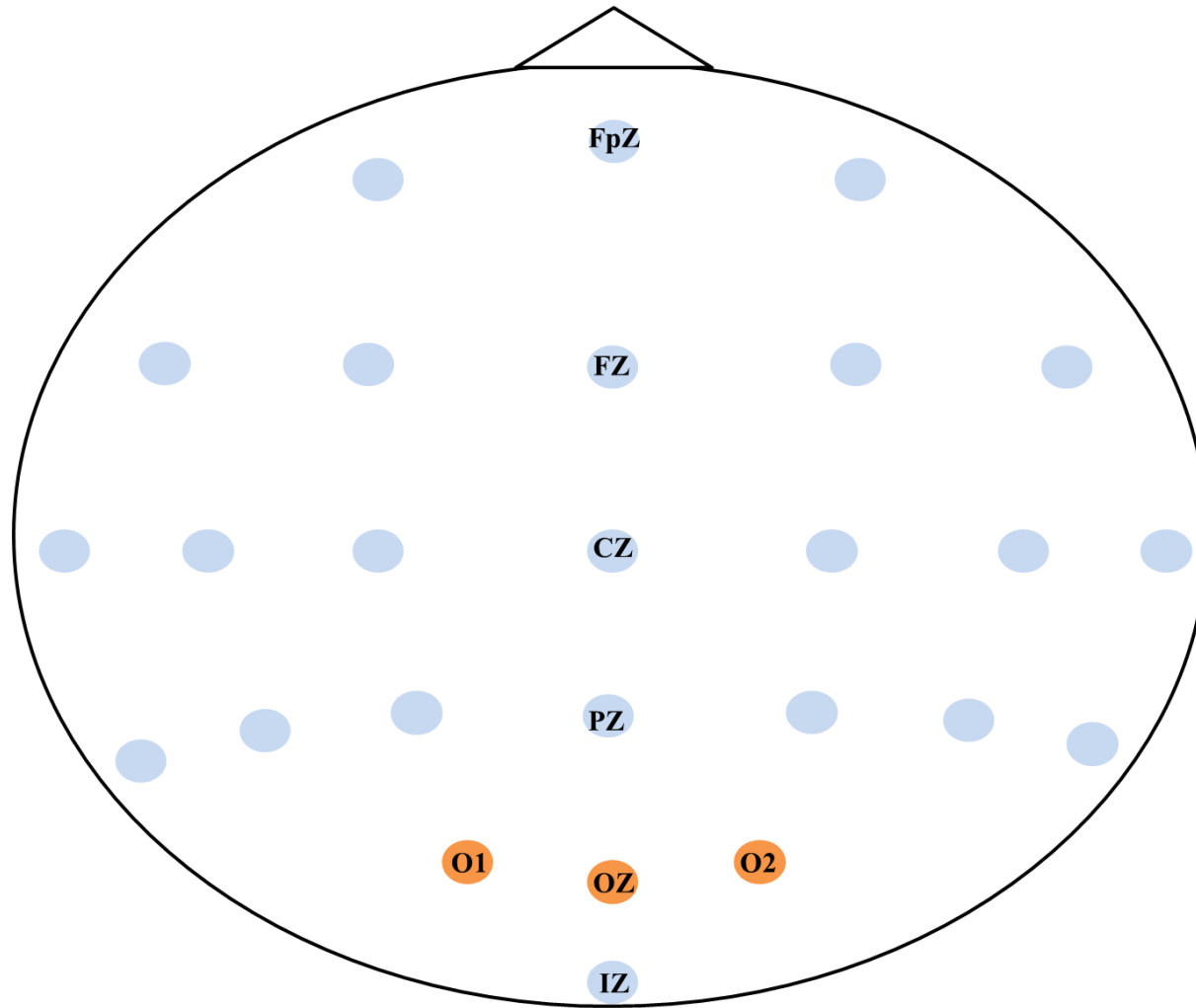


Figure 5.2, Simplified schematic of the electrode montage used during recording. The orange sections indicate the electrodes used for the visual evoked potential analyses.

Although age related changes in retinal efficiency, and conditions such as presbyopia and cataracts, are often corrected by either the use of refraction, or by surgical operation, the eyesight of ageing participants cannot be assumed to be of the same quality or have the same reliability as that of healthy young individuals. In the present study the inter-ocular difference in the P1 latency between left and right eyes was used to identify effects of residual eye disease. To maximise the data available for comparison, and to provide only comparisons of natural retinal processing (without eye disease), the data entered to the group analyses were selected based on the matching of latencies. If left and right eye recordings were within 10ms of each other the inter-ocular difference was considered acceptable and the recording of both eyes simultaneously was used. In the case that there was a difference of greater than 10ms the measurements were taken from the eye with the shortest latency. Participants were excluded if the P1 latency for all conditions exceeded the group mean by three standard deviations.

5.2.4 Statistical Analyses

Covariates

Age, visual acuity, and levodopa dose (in PD/PDD) have all been previously linked to changes in the VEP component measurements (Bartel & Vos, 1994; Chiappa, 1997). These variables, and additional variables motor severity (UPDRS total score), and disease duration, were tested as predictors of variance in the VEP component measurements using the process described in **Chapter 3**.

Between Groups Comparisons

Normally distributed amplitudes and latencies for the N1, P1, and N2 component, with no covariates were compared using independent samples t-tests. Those with covariates were compared using one way analysis of covariance (ANCOVA), controlling for the correlated variable(s). Non-normally distributed data were compared using the Mann-Whitney U test. Significance was reached at a probability of $p < .05$, and supported using appropriate effect sizes and the 95% confidence interval.

Within Groups Comparisons

In other conditions characterised by bottom-up disturbances the VEP demonstrates a gradual increase in P1 latency (e.g. multiple sclerosis, Asselman et al, 1975; Halliday et al, 1973), or a global decrease in amplitude (e.g. retinal disease, Chen et al, 2012). It was hypothesised that if VH in PDD involve contributions from bottom-up dysfunction it might be possible to identify a physiological marker based on changes evident in the VEP. In the PDD group the

VEP component measurements were tested for a relationship with VH severity (NPI hallucinations subscale frequency*severity; NEVHI derived score) using Spearman's correlations. Comparisons for patient and carer ratings were performed separately. For each set of comparisons (NPI hallucinations subscale & Latency; NPI hallucinations subscale & Amplitude; NEVHI & Latency; NEVHI & Amplitude) p values were corrected for multiple comparisons using the Bonferroni method ($\alpha = 0.016$).

5.3 Results

5.3.1 Normality

Control and PDD measurements of latency were all normally distributed. Control measurements of amplitude were normally distributed for the N1 and P1 components. All remaining measurements were non-normally distributed.

5.3.2 Covariates

Investigation of covariates revealed that age was associated with increasing N2 latency in the control group ($\beta = .513, p = .035$) but not the PDD group ($\beta = -.056, p = .68$). In light of this, and that age has previously been shown to affect the latency of the VEP response (Shaw et al, 1980) the N2 data was corrected for age during between group's comparisons. No other variables acted as predictors of the VEP component measurements. See **Table 5.1**.

5.3.3 Between Groups Comparisons

Group latencies and amplitudes are summarised in **Table 5.2**. For a visualisation of the visual evoked potential waveforms please see **Figure 5.3**.

P1 Amplitude and Latency

The Mann-Whitney U test revealed that the PDD amplitudes were significantly lower than in the control group ($U = 92, Z = -2.2, p = .028, r = -.37, CI \text{ lower: } .07; \text{ upper: } 3.1$). However, the independent samples t-test did not reveal any differences between the groups in terms of their P1 latency ($t(34) = -.8, p = .429, d = -.27, CI \text{ lower } -7.2; \text{ upper } 3.2$).

N1 Amplitude and Latency

Comparisons with the Mann-Whitney U test revealed a significant reduction in the PDD N1 amplitude relative to the control group ($U = 99.5, Z = -1.965, p = .049, r = -.33, CI \text{ lower: } -1.1; \text{ upper: } 0$). The narrow width of the confidence interval suggests that the precision at which the true median can be located is very high. However, the proximity to the null value

(zero) infers that the medians are only narrowly avoiding symmetry and thus the N1 amplitude comparisons should be treated somewhat cautiously. When comparing the N1 latencies independent samples t-test did not detect any significant differences between the groups ($t(34) = -.457, p = .651, r = -.12, d = -.245, 95\% \text{ CI lower: } -8.1; \text{ upper: } 5.1$).

N2 Amplitude and Latency

The Mann-Whitney U did not reveal any significant differences between the group medians for the N2 amplitude measurement, $U = 118, Z = -1.379, p = .168, r = -0.2, \text{ CI lower: } -0.1; \text{ upper: } 1.6$). One way ANCOVA demonstrated a significant main effect of group on N2 latencies, ($F(2, 33) = 4.678, p = .016, r = -.45, d = 1, \text{ CI lower: } -22.16; \text{ upper: } -1.05$). This effect showed that the N2 latency was increased in the PDD group relative to the control group, and was supported by a large effect size although the 95% CI values were particularly wide.

5.3.4 Effects of Visual Hallucination Severity

In PDD patients the P1 latency demonstrated a significant negative correlation with both measures of VH severity (NPI hallucinations subscale, $r_s = -.745, p = .0002$; NEVHI, $r_s = -.788, p = .00006$), **see Figure 5.4**. Visual hallucination severity did not correlate with any of the other remaining component amplitude or latency measurements. As further post-hoc analysis the PDD group were divided into two sub-groups to describe the P1 latency relationship with the experience of VH described as a dichotomy (i.e. current or past history of VH vs. no history of VH). Mann-Whitney U contrasted $n = 7$ participants who did not report VH with $n = 12$ participants who had reported experiencing VH, revealing that the ranks of the latency were significantly lower in those who experienced VH ($U = 8, Z = -2.876, p = .002, r = 0.97, 95\% \text{ CI lower: } -18.55; \text{ upper: } -4.24$).

Table 5.1, Summary of the covariate analyses for the visual evoked potential (VEP) component measurements of amplitude and latency. Significant results are highlighted in bold.

Group	Component	Measurement	Age		Visual Acuity		Levodopa Dose		UPDRS		Disease Duration		
			<i>rs</i>	β	<i>p</i>	<i>rs</i>	<i>p</i>	<i>rs</i>	<i>p</i>	<i>rs</i>	<i>p</i>	<i>rs</i>	<i>p</i>
<i>Controls</i>	N1	<i>Amplitude</i>	0.194		0.455	0.044	0.866			0.436	0.08		
		<i>Latency</i>	0.21		0.42	0.133	0.612			0.167	0.521		
	P1	<i>Amplitude</i>	-0.261		0.312	-0.126	0.629			-0.277	0.282		
		<i>Latency</i>	0.397		0.115	0.045	0.862			0.078	0.765		
	N2	<i>Amplitude</i>	0.209		0.42	0.148	0.57			0.139	0.596		
		<i>Latency</i>	0.5	0.513	0.04	0.118	0.652			0.134	0.607		
<i>PDD</i>	N1	<i>Amplitude</i>	-0.166		0.498	-0.318	0.198	0.179	0.464	0.159	0.516	0.154	0.53
		<i>Latency</i>	0.137		0.575	0.086	0.735	-0.221	0.363	-0.167	0.494	-0.184	0.45
	P1	<i>Amplitude</i>	0.152		0.533	0.332	0.179	-0.148	0.546	-0.191	0.432	-0.071	0.772
		<i>Latency</i>	0.055		0.823	-0.001	0.998	0.102	0.677	-0.296	0.219	-0.073	0.767
	N2	<i>Amplitude</i>	-0.37		0.881	-0.199	0.427	0.073	0.768	0.172	0.481	0.041	-0.157
		<i>Latency</i>	-0.1	-0.056	0.682	-0.283	0.255	-0.008	0.973	0.025	0.918	0.133	0.587

Table 5.2, Summary of the group amplitudes and latencies for each component. P values are shown to highlight significant differences.

Component	Mean Amplitude (\pm)			Mean Latency (\pm)		
	<i>Control</i>	<i>PDD</i>	<i>p</i>	<i>Control</i>	<i>PDD</i>	<i>p</i>
<i>N1</i>	-1.37 (.95)	.78 (.75)	.049 †	88.77 (8.3)	90.3 (11.2)	.65 ‡
<i>P1</i>	3.94 (2.6)	2.21 (1.7)	.028 †	124.5 (7.8)	162.5 (9.6)	.43 ‡
<i>N2</i>	-1.8 (1.5)	-1.04 (.82)	.17 †	126.6 (7.6)	175.6 (15.8)	.02 ‡*

† = Mann-Whitney U test

‡ = Independent samples t-test

* = Corrected for age

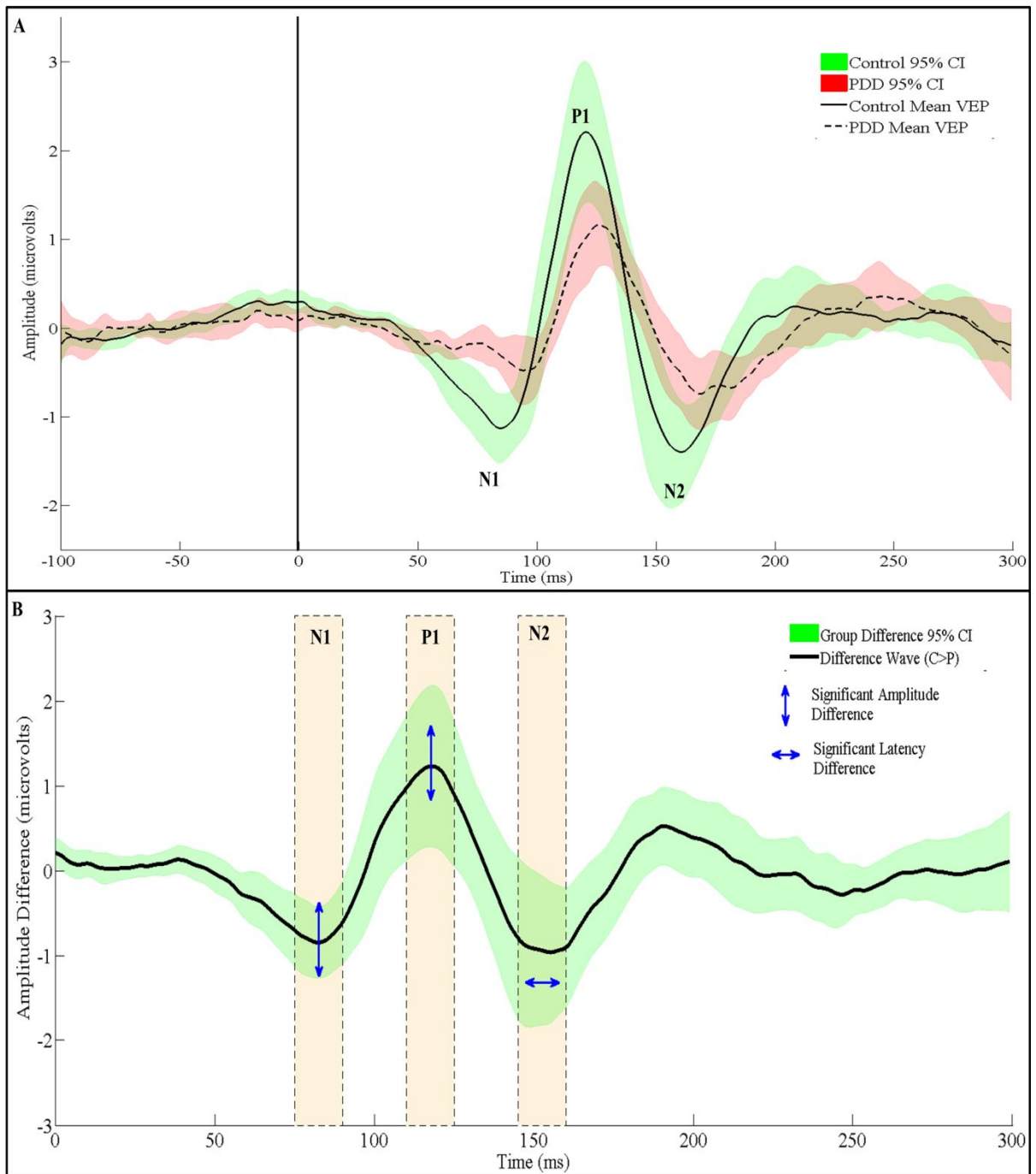


Figure 5.3, A) Comparison of Control and PDD visual evoked potential (VEP) waveforms with group confidence intervals. Waveform components are labelled. B) Significant differences demonstrated using the difference waveform (Controls – PDD). Blue vertical arrows represent a significant difference in component amplitude, were as blue horizontal arrows represent a significant difference in component latency. The boxes around each component serve to highlight the time window in which the peak occurred.

Relationship Between Visual Hallucination Severity and VEP P1 Latency

Carer vs Patient Ratings of Severity

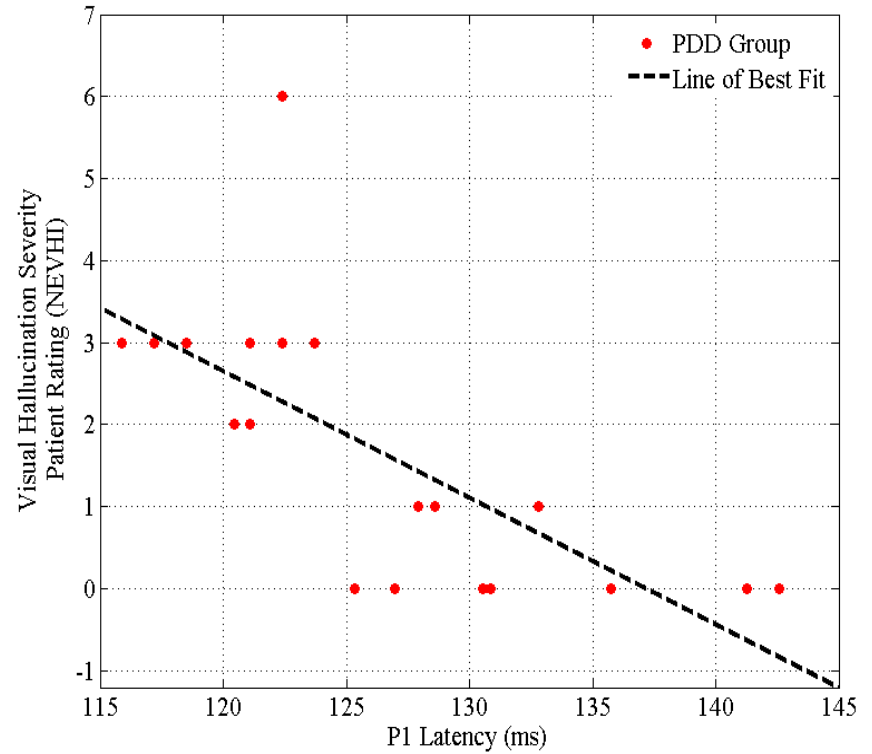
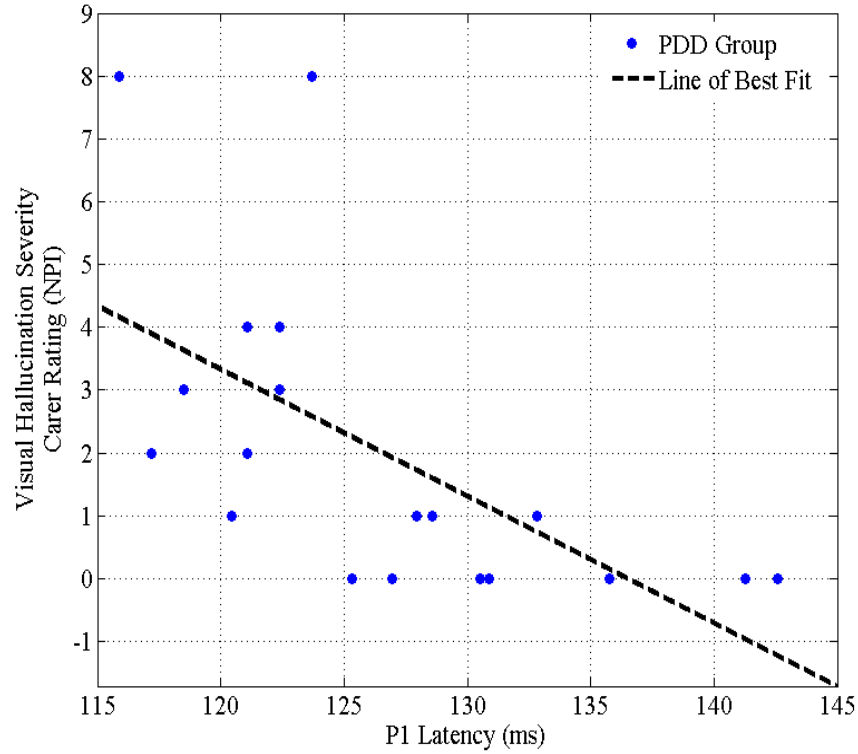


Figure 5.4, Comparison of Neuropsychiatric Inventory (NPI hallucinations subscale) and North East Visual Hallucinations Interview (NEVHI) ratings of visual hallucination severity and their relationship with the P1 component latency.

5.4 Discussion

In this study the pattern reversal VEP was used to study the correlates of early bottom-up processing in PDD with a varying extent of VH severity. The aim of this investigation was to characterise the neurophysiological components of early visual processing in PDD and to draw inferences about what their functional properties might reflect in terms of both pre-striate transmission and the sources of cortical processing proximal to V1. As discussed below, the results lend support to the notion that the primary visual cortex remains broadly intact in PDD, similar to what has been reported in DLB (Taylor et al, 2011), and further strengthen the recent claim that pre-striate transfer of visual information is unaffected by Lewy body pathology (see below for further elaboration; Erskine et al, 2015; Yamamoto et al, 2006). Despite literature suggesting that the dosage of levodopa (e.g. Bodis-Wollner & Yahr, 1978), and increasing age impact on the VEP, in the present study these factors did not affect measurements of the VEP (except for the N2 latency which was associated with age). Interestingly, and in contrast with a-priori hypotheses, increasing VH severity was found to show an inverse relationship with the P1 latency.

5.4.1 *Markers of Pre-Striate Communication*

By and large the history of clinical VEP recordings in PD paints a picture of delays in conduction velocity from the retina to V1 (Bodis-Wollner, 1978; Kupersmith et al, 1982; Bandini et al, 2001), in tandem with impaired clarity of the visual input (e.g. lowered visual acuity; Archibald et al, 2009). In these cases the P1 component is much more latent when compared to typical control scores, and thus interpreted as a marker of impaired visual information transfer. However, estimates of the P1 source suggest that this potential is generated by a number of inputs in the posterior visual cortex, possibly as a result of rapid cross-talk between V1 and V2 (Barnikol et al, 2006; DiRusso et al, 2005). For example, Pins and ffytche (2003) found that the combination V1, the lateral occipital cortex, and the medial occipital cortex, all contributed to the generation of the visual P1 response (Pins & ffytche, 2003). On the other hand the N1 is estimated to be generated by thalamocortical projections from the LGN to V1 (DiRusso et al, 2005). Based on the estimated population of neurons contributing to the N1 source it is thus likely to be a more temporally accurate marker of information arriving at V1. However, due to its less obvious nature this component is often unreported in clinical cases. In the current study the N1 latency was not significantly different between the groups, and did not demonstrate a trend related to VH severity. Although it is not possible to directly estimate the activity of LGN projections using EEG the lack of group

latency differences in the N1 component indirectly supports the notion that conduction delays in the pre-striate pathways in PDD are limited regardless of VH severity. Although there are known differences at the level of the retina (Nightingale et al, 1986; Archibald et al, 2009), and in the gating properties of the primary visual cortex (Perry et al, 1990; McKeith et al, 2004), relatively little is understood about how visual information is transferred to V1 in Lewy body dementias. Several recent pathological examinations have described a lack of Lewy body pathology in the LGN and the primary visual pathway (Erskine et al, 2015; Yamamoto et al, 2006), the implication of which is that there are no structural or neurochemical changes occurring which alter the conduction velocity along the optic nerves towards V1 (save for changes in the retinal nerve fibre layer thickness (Lee et al, 2014), although this has not been considered in the context of the VEP in PDD). One interpretation is that the findings in the present study of similar N1 latency measurements between the groups may imply that intact conduction could be one part of a set of pre-requisites for the experience of VH.

In contrast the amplitude of the N1 and P1 components were significantly reduced in the PDD group relative to controls, as were their visual acuity scores. Previous interpretations of reductions in pattern reversal amplitudes have implicated diminishing visual acuity (Chen et al, 2012). In PD a number of visual abnormalities have been reported, accounting for age related retinal changes (Archibald et al, 2009) such as poor visual acuity (Jones et al, 1992; Holroyd et al, 2001), low contrast sensitivity (Regan & Neima, 1984; Bodis-Wollner et al, 1987), and reduced sensitivity to colours (Price et al, 1992; Pieri et al, 2000). Although alterations in cortical processing are likely to play a role, studies of the neurochemical and psychophysical mechanisms of these impairments strongly support changes within the retinal cells (Bulens et al, 1987; Hutton et al, 1993; Rodnitzky, 1997; Büttner et al, 2000; Nguyen-Legros et al, 1994; Nguyen-Legros et al, 1988; Inzelberg et al, 2004; Nowacka et al, 2015).

Recently Nowacka and colleagues (Nowacka et al, 2015) contrasted electroretinogram (ERG) amplitudes with measures of retinal thickness, and patient reports on dopamine-dependent visual functions, in early stage PD. Although their findings did not reach significance for visual acuity, or retinal thickness, there was a reduction in the amplitudes of the scotopic α and β -waves of the ERG, which is thought to be regulated by dopaminergic signalling (Shulman & Fox, 1996; Krizaj et al, 1998). Further, as the peak time of the ERG oscillatory potentials increased PD patients were more likely to report difficulties in light adaptation and contrast sensitivity. The reduction in amplitude of the α and β -waves points to a disturbance

of photoreceptors at multiple layers of the retina, which would create problems with adaptation to different light states. Due to the reduced level of information reaching the primary visual cortex there would follow a reduction in the density of neurons required to process the incoming signal (N1). This would then be reflected in subsequent cortical processing (P1, N2). Conversely, compensatory models are gaining increasing traction to explain cortical processing changes in dementia (Coyle et al, 2015; Rowan, 2011); thus despite the physical decline of the early visual system significant compensatory changes may also be occurring in an attempt to normalise conduction times as the stability of these are essential for normal cortical processing. However, clarifying this would require a longitudinal study of the VEP contrasted between those patients who would go on to develop VH versus those who would not.

An alternative proposal is that the changes in contrast sensitivity act to alter the thresholds required for access to conscious perception (Pins & ffytche, 2003). Here the amplitude change would reflect a downshift in the extent of resources applied for processing, as a result of changes to the psychophysical mechanisms governing early visual attention, scaled by the input's relation to the visual threshold (Pins & ffytche, 2003; Lu & Doshier, 1998). Although this alternative explanation is perfectly plausible for explaining mechanisms of visual attention and access to conscious experience the paradigms used by these studies are more finely tailored towards the study of higher visual cognition than the methods used in the current study. The pattern reversal paradigm used in the current study also presents a high luminance, and balanced contrast stimulus to the participant, with no active attention required to perceive the pattern. Here the potentials measured reflect processing in response to the onset and offset of light emitted from the display. The possibility remains that with a more nuanced design than the one presented here it would be feasible to measure the consequences of poor photoreceptor activation for conscious perception (e.g. Pins & ffytche, 2003), although the choice of a simplistic passive stimulus has significant advantages in cognitively impaired participants as it avoids the confound of potential task dependent performance effects.

In the current study the visual acuity, N1 and P1 amplitudes were unrelated to disease duration, motor severity, or age, implying that retinal changes were driven primarily by PDD pathology. In addition they were not related to VH occurrence or severity. However, the pairing of bottom-up impairments with compromises in the quality of the information being presented to higher cortical visual areas might place an individual with PDD in an “at risk”

state for VH. The co-presence of other factors such as dysfunctions in attention/executive control may then be required for the manifestation of VH – at least in PDD. This integrative interpretation contrasts with the visual deprivation/release models which are believed to underpin the generation of VH in conditions such as Charles Bonnet syndrome (e.g. Siatkowski et al, 1990; Burke, 2002).

5.4.2 Primary Visual Cortex Communication

The lack of P1 component latency difference between groups was unexpected due to the previous suggestion in the literature that P1 latencies were slowed as a result of PD pathology. However, the intriguing inverse relationship with VH severity suggests that factors contributing to P1 latency changes in PDD may be complex. The separation by Spearman's correlation indicated that as the severity of the VH increases the P1 reaches peak latencies similar to that of the control group. Given what is known of the cognitive profile of PDD (Mosimann et al, 2004; Hepp, et al, 2013; Barnes & Boubert, 2008; McKeith et al, 2005; see **Chapters 1 & 4**), and the decline of the executive systems controlling communication within the visual system (Sanchez-Castaneda, et al 2010; Shine et al, 2014), an improvement in function seems unlikely. Nevertheless, this raises the possibility that increasing VH severity in PDD may be accompanied by visual subsystem changes to compensate for reduced efficiency at a higher level.

Certainly a number of other markers already suggest that abnormal functioning of the visual cortex occurs within a structurally intact environment (Dey et al, 2015; Morris et al, 2015; Higuchi et al, 2000; Fujishiro et al, 2012; Colloby et al, 2002). The change in latency may suggest that with increasing VH severity there is a change in the influence of inhibitory control at the primary visual cortex. Recent neuropathology in DLB with VH has ruled out a reduction in the density of occipital interneurons (Dey et al, 2015; Morris et al, 2015), pointing instead towards an alteration in communication via a reduction in the number of postsynaptic gamma-aminobutyric acid (GABAergic) markers (Morris et al, 2015) and is supported by fMRI and TMS data suggesting a relative loss of visual cortical inhibition in DLB hallucinators (Taylor et al. 2015; Terhune et al, 2015). The consequences of this in terms of the VEP would be a reduction in the time taken for postsynaptic potentials to summate, resulting in a reduced P1 latency. However, to disentangle whether or not this is a compensatory effect would require a mix of longitudinal cognitive, physiological, and pathological data which is beyond the scope of the current study. However, mega press

imaging of the subjects in the current study (see **Chapter 3**) will hopefully help to provide an insight into the GABAergic concentrations of the cohort being described.

The difficulty with interpreting this finding is due to the vast wealth of changes that occur within the visual system and the paucity of developmental evidence to demonstrate when these changes occur and how they are all linked. Nonetheless, at a larger scale a mechanism of compensatory disinhibition is in keeping with the integrative architecture proposed by Collerton (Collerton et al, 2005) and Shine (Shine et al, 2012). However, in addition to the changes in top-down attention it seems fitting to propose that there is also a change to bottom-up attention. For example, the models of Collerton and Shine both suggest that there exist changes which alter the efficiency of information binding into the correct percept. The physical manifestation of this, according to Shine et al. is the over reliance on the default mode network (DMN) following disconnection between the dorsal and ventral attention networks (DAN, VAN; Shine et al, 2014). The consequence of this is increased mind wandering in the absence of properly orienting attention towards salient features of the environment/stimuli. When the input is of lower clarity it would follow that there would be less correct matches between the elements of the signal and their intended representations (Pajani et al, 2015; Collerton et al, 2005). Recently, the study of eye tracking has been used to demonstrate the gaze control and frequency of saccades in patients with PD (Stuart et al, 2015). PD patients were shown to make less frequent saccades reflecting less efficient updating of their visual environment. This was linked to poorer cognition, making the likelihood of missing small details greater as the disease progressed. In the context of a predictive coding framework, such as that alluded to above (Pajani et al, 2015; Shine et al, 2014, 2012; Collerton et al, 2005), the combination of less frequent updating with compromises in the quality of retinal output would drastically increase the chances of generating false imagery. Altering the level of inhibition might enhance visual detection by allowing action potentials to summate faster which could have a positive effect in reducing perceptual matching errors. Conversely, an unfettered early visual system may produce upstream visual information with significant noise which could actually exacerbate matching errors.

Despite the presence of this phenomenon there are still numerous visual complaints in this cohort, and signs of dysfunction in the feedforward processing of visual information evidenced by the slowing of the N2 latency (likely a correlate of reduced white matter anisotropy, e.g. Hattori et al, 2012; Melzer et al, 2013). Importantly VH still occur in many

of these patients, suggesting that if any form of compensation is occurring, it is only effective to a certain degree.

5.4.3 Limitations

The primary limitation of the analyses presented in this chapter is the size of the samples used. In both groups the total numbers of participants is relatively small, despite using more than 100 trials per subject to improve the signal to noise ratio in the VEP measurements. The variance within each group would be reduced in a larger sample, further helping to improve the confidence in the accuracy of each comparison. Additionally, correlations with small numbers are more likely to reach significant values based on small numbers of outliers and whilst the study is exploratory there are issues of multiple comparisons. A strength of these analyses is the proven reliability of the VEP response. This method has proven to be a robust measurement of visual information transfer, with little variance within individuals (Sarnthein et al, 2009). Regardless, a larger sample will be required in future analyses to determine the accuracy of the conclusions presented here.

A further limitation of this investigation is the range of VH severity scores. The ideal primary comparison would be to compare between absolute groups of VH and no-VH, relative to controls. Due to the sample sizes recruited during the timeframe of the study this comparison was limited to a correlation with patient and carer ratings of VH severity. The relative strengths of this are described in **chapter 4**, however, comparison by this nature would require the recruitment of PDD participants with a wider range of VH severity scores than is currently available. This prevents a more decisive statement being made about the nature of visual system physiology in relation to the severity of VH. Future work should aim to expand the range of VH severity scores to determine if the correlation continues or if compensation begins to fail with more extreme severity, and loss of insight.

5.4.4 Conclusions

The outcome of this investigation posits that conduction delays in bottom-up visual information transfer between the retina and the primary visual cortex remains broadly intact in patients with PDD. However, the effects of PD pathology within the retina might be acting to reduce the quality of the information fed into the visual system. The trend for decreasing P1 latencies with increasing VH severity might reflect a mechanism that attempts to compensate for the combination of poor visual input and the decreasing cognitive capacity to accurately process visual information. However, more detailed PDD samples will be needed to

confidently interpret this effect. Whether this is an epiphenomenon or causally related to VH remains to be explained. Future work should focus on a multimodal approach to understanding the circuitry controlling bottom-up attention in the primary visual cortex and how this is altered over the development of PD/PDD.

Chapter 6 Transcranial Magnetic Current Stimulation Evoked Potentials for the Study of Visual Hallucinations in Parkinson's Disease with Dementia

"I've seen things you people wouldn't believe... All those moments will be lost in time, like tears in rain"

- Blade Runner, H. Fancher (1982)

6.1 Introduction

Advances in our understanding of both the pathological substrates, and the cognitive profile associated with visual hallucinations (VH) have resulted in the consensus that this symptom arises from dysfunctional and distributed network behaviour, in particular, those networks associated with top-down control (Collerton et al, 2005; Shine et al, 2011; Diederich et al, 2004; O'Callaghan et al, 2014; Delli-Pizzi et al, 2014), rather than aberrant activity in isolated brain regions. From the perspective of Parkinson's disease with dementia (PDD) more generally there is widespread disruption of the extra-striate cortex, as well as the sub-cortical systems responsible for inter-cortical communication (Diederich et al, 2015). At the same time there is a reduction of grey matter in the occipital, temporal, and parietal cortices (Burton et al, 2004), and reduced metabolism at the occipital cortex (Colloby et al, 2002). Despite these changes, and the fact that VH are a common symptom in PDD, patients do not demonstrate an absolute loss of visual function, rather they have a reduced visual efficiency (Mosimann et al, 2004; Urwyler et al, 2015; Uchiyama et al, 2012).

Input to the visual system in PD with and without dementia has been demonstrated to be impoverished with reductions in visual acuity, and direct physical changes to photoreceptor cells within the retina (Archibald, 2009; Holroyd et al, 2001; Nowacka et al, 2015). However, not all patients with PDD will experience VH. This would imply that additional factor(s) are required for VH genesis. However, at what stage(s) in the stream of visual processing these factors are located is still unclear. The evidence available is highly supportive of an attention based impairment, whereby the management of processing loops is less efficient resulting in sensory information (in this case visual) being bound incorrectly (Shine et al, 2014; Shine et al, 2015; Franciotti et al, 2015). However, the distribution of pathology suggests that any information passed through the ventral and dorsal visual streams, at any stage, might be exposed to alterations and bias as a result of disturbances in normal visual processing. In this case the information fed forwards would potentially be degraded, and lack fidelity, and thus

impact upon the ability of executive processes to appropriately bind the information. One way of exploring this is by testing for a temporal marker of cortical synaptic activity. Although methods such as electroencephalography (EEG) are limited to interpretations about very broad populations of neurons, the study of how and when these populations respond in relation to a stimulus could help to add a much needed temporal resolution to the aetiology of VH in PDD.

When applied to the cortex the pulse from transcranial magnetic stimulation (TMS) activates a network of functionally connected structures (Garcia et al, 2011), which can be studied as an evoked potential using stimulation during concurrent EEG (Taylor, Walsh, & Eimer, 2008; Miniussi & Thut, 2010; Taylor et al, 2010; Garcia et al, 2010; Rogasch et al, 2014; Korhonen et al, 2010). The components of the TMS evoked potential (TEP) reflect the spatio-temporal response of the cortex following the stimulation with patterns of activation typically following expected cortical hodologies. When applied to occipital cortex the result is an approximation to basic visual processing but one which is free of an external stimulus and any influencing factors arising from, for example, the pre-striate transfer of information. At each TEP component the measurement of the amplitude and latency provides an estimate of how the contributing populations are behaving. As well as being used for inferences about the general physiology of the visual system it is possible to observe how these populations of neurons respond during active visual processing. In addition as the TMS stimulation intensity is increased the individual is likely to experience an artificial sensation of light known as a phosphene (Marg & Rudiak, 1994; Kammer, 1999; Kammer et al, 2005). The precise origin of this phenomenon is still debated but is thought to represent an extended activation of the visual system (Caparelli et al, 2010). By comparing the instances of phosphenes versus without it becomes possible to study how the neuronal populations represented by the TEP respond to increased attentional demands (Taylor et al, 2010; Bagattini et al, 2015).

Phosphenes also allow for the study of visual processing at multiple stages, including vigilance towards incoming visual information (e.g. Romei et al, 2008), stimulus gain control (e.g. Chaumon et al, 2014), and their temporal emergence (e.g. Taylor et al 2010).

Phosphenes have previously been used in studies as a measure of both cortical excitability and the structural integrity of the visual system in dementia with Lewy bodies (DLB; Taylor et al, 2011). However, concurrent TMS and EEG has not yet been utilised in a Lewy body dementia (LBD) population.

In this investigation we applied concurrent TMS and EEG to the occipital cortex of PDD patients and healthy controls to observe patterns of visual system synaptic activity along a spectrum of VH severity (see **Chapter 4**). Both the spatio-temporal response to TMS and the individual stimulation profiles were analysed to determine if the visual system neurons in PDD are inherently dysfunctional or if disrupted communication is primarily the result of top-down executive impairments.

6.2 Methods

6.2.1 Participants

TMS evoked potentials (TEP) were recorded from $n = 17$ healthy controls (mean age 75.47 years \pm 5.4), and $n = 21$ Parkinson's disease with dementia (PDD) patients (mean age 73.43 years \pm 5.66). The TEP analyses were split into two stages: general TEP waveform (only no-phosphene trials); phosphene related TEP waveform (discussed further below).

In order to reliably estimate the independent component structure of the mixed EEG signal (see **Chapter 3**) the algorithm should be presented with a minimum number of data points per channel equivalent to twenty multiplied by the number of channels squared (Onton et al, 2006; see **Equation 6.1**).

$$ICAdata = 20 * (Nchans^2)$$

Equation 6.1, Determination of the minimum number of data points required for reliable/stable estimation of mixed signal independent components.

Using the epoch sizes described below each trial contained 4194 data points, therefore a minimum of 78 trials (excluding any rejected prior to independent components analysis, ICA) per participant were required to ensure that the minimum number of 327680 data points was presented to the ICA algorithm ($20*(128^2)$). Individuals who did not reach this minimum trial number were not included in the analyses further (two controls and four PDD participants). One PDD participant was excluded due to an anatomical abnormality on their structural MRI scan (see **Chapter 4**). The final comparison of the general TEP waveform therefore included $n = 15$ controls (mean age 76.4 \pm 5.01), and $n = 16$ PDD patients (mean age 72.75 \pm 5.91).

A total of $n = 9$ controls (mean age 74.78 \pm 4.3), and $n = 9$ PDD patients (mean age 75.11 \pm 6.7) reported phosphenes on at least 50% of trials during the stimulation paradigm and were used in the comparison of the phosphene related TEP's. Partial phosphene perception (semi-regular, fewer than 40% of trials), was reported in $n = 3$ PDD participants. The reports of

these participants were included for the comparison of stimulation characteristics and phosphene complexity (a total of $n = 12$ PDD patients (mean age 74.92 ± 5.84)).

6.2.2 Data Acquisition

All participants received occipital cortex TMS whilst simultaneously recording their cortical response via the 128 channel EEG (described in **Chapter 3**). The TMS coil was guided using neuronavigation to improve the reliability of stimulation locations between trials (see **Chapter 3**). Individual coil positions for each participant were recorded as the percentage horizontal and vertical distances from electrode Oz. The protocol used for determining phosphene threshold (PT) in participants is described in **Chapter 3**.

For those who reported seeing phosphenes the actual stimulation intensity (SI) was the same as the PT. For those who did not report seeing phosphenes an arbitrary PT of 101% was used for group comparisons of PT, given to reflect the possibility of phosphene perception being limited by the devices being used (Taylor et al, 2011; Kammer et al, 2001). In these non-responders the SI was set at 75% of the stimulator output for the purposes of eliciting the TEP.

The phenomenology of any experienced phosphenes was rated using a six point system (e.g. Taylor et al, 2011), with one point assigned for each of the following: two dimensional geometric shape; motion; colour (not grey); complicated shape/colour; texture; visual hallucination like appearance. The sum of these scores was taken as the individual's phosphene complexity (PC) rating. Phosphene complexity has previously shown a negative relationship with PT, with lower PT yielding higher PC scores (Taylor et al, 2011) and has been posited as a crude measure of the excitability of the different visual regions along the propagation route of the TMS pulse (Taylor et al, 2011; Taylor et al, 2010). In patients with DLB the relationship between PC and PT has been shown to be stronger than in control participants (Taylor et al, 2011) representing a possible marker for higher visual activity during tasks involving TMS. The measure of PC was replicated in the current study to investigate a relationship between PC and the physiological response to visual cortex stimulation.

During the TMS session the participants were asked to provide regular reports on feelings of discomfort. This included how dizzy or nauseous they felt, as well as any feelings of pain or headache. The experiment was terminated if the participant reported any feelings of discomfort which they felt would hinder them from being able to concentrate on the task.

6.2.3 Data Analysis

For the removal of TMS artefacts the data were split into epochs of length 2048ms (stimulation \pm 1024ms), artefacts were then identified and removed using the protocol described in **Chapter 3**. Artefact free data were then filtered using a 0.1 to 45Hz bandpass filter and split into epochs of length 800ms (200ms pre-stimulus, 600ms post-stimulus). The epoch size was chosen based on recent reports that suggest event related potential activity occurs until \sim 500ms (Taylor et al, 2010; Garcia et al, 2011; Herring et al, 2015; Bagattini et al, 2015). Because this method had not yet been performed in old aged or PDD populations the epoch was extended to 600ms post-stimulus to account for age and disease related slowing in information transfer within the cortex (e.g. Hattori et al, 2012; Li, Gratton et al, 2013; Watanabe et al, 2013; Park et al, 2012; Bidelman et al, 2014).

With the study of the TEP being fairly new little is understood about the sources generating the response and its components, or their functional relevance. The challenge is to measure the response appropriately so as to maximise the potential for interpretation at a between groups level. Traditional peak based measurements provide the data to compare the maximal functional response from a population of neurons within a fixed window in time. This method focuses on the most obvious functional responses relative to the stimulus, allowing for inferences about the contributions of neurons at a given point in time. However, this method is static, falling short of providing a full account of the response to the stimulus, and fails to identify important differences that might be missed by such conservative hypothesis testing. In recent years advances in statistical approaches to EEG analysis have allowed for a more data driven hypothesis testing (e.g. Maris & Oostenveld, 2007; Bagattini et al, 2015). These approaches consider the data on a time-point by time-point basis, iterating through the waveform to find clusters of significant activity. This provides a useful, more experimental approach to testing times series differences, and can be expanded to further consider differences between clusters of electrodes (Maris & Oostenveld, 2007).

In order to maximise the temporal resolution, and in doing so the extent of physiological comparisons, two measurements of the general TEP response were performed: a window based method, and a time-point by time-point (mass-univariate) method.

Window Method

Because there is a paucity of research focussing on the TEP and its component structure periods of prominent activity were identified using the global field power (GFP; see **Chapter**

3) rather than using literature defined windows. Measurement windows were defined as the peak latency for each of the GFP maxima ($n = 4$) ± 10 ms. Amplitudes were measured, independent of their polarity, by taking the mean of all data points within each window at each electrode. Latencies for each component were measured by taking the latency of the peak within each window per electrode. The electrode montage was then split into three regions of interest (ROI) for between groups comparisons. These were based broadly on scalp positions overlying the occipital, temporal (ventral stream), and parietal (dorsal stream) cortices (see **Figure 6.1 & Table 6.1**). For the comparison of the general TEP response only trials without phosphenes were used. For the comparison of phosphene evoked potentials between groups phosphene condition waveforms were subtracted from non-phosphene waveforms to create a difference wave. The difference waveforms were measured using the same approaches as above.

Table 6.1, Regional electrodes used for the transcranial magnetic current stimulation (TMS) evoked potential (TEP) analyses.

Region of Interest	Electrode Labels					
<i>Occipital</i>	'POz'	'PO5'	'PO7'	'PPO1'	'PPO6h'	'POO4h'
	'O1'	'PO3'	'PO8'	'PPO2'	'PPO10h'	'POO10h'
	'Oz'	'PO4'	'PO9'	'PPO9h'	'POO9h'	'OI1h'
	'O2'	'PO6'	'PO10'	'PPO5h'	'POO3h'	'OI2h'
<i>Parietal</i>	'C3'	'P3'	'CP3'	'P10'	'CPP6h'	
	'Cz'	'Pz'	'CPz'	'CCP5h'	'CCP1h'	
	'C4'	'P4'	'CP4'	'CCP3h'	'CCP2h'	
	'CP5'	'P8'	'P5'	'CCP4h'	'CPP1h'	
	'CP1'	'C5'	'P1'	'CCP6h'	'CPP2h'	
	'CP2'	'C1'	'P2'	'CPP5h'		
	'CP6'	'C2'	'P6'	'CPP3h'		
	'P7'	'C6'	'P9'	'CPP4h'		
<i>Temporal</i>	'FT7'	'FT9'	'FFT7h'	'FTT8h'		
	'FT8'	'FT10'	'FFT8h'	'FTT10h'		
	'TP7'	'TPP9h'	'FTT9h'	'TPP7h'		
	'TP8'	'TPP10h'	'FTT7h'	'TPP8h'		

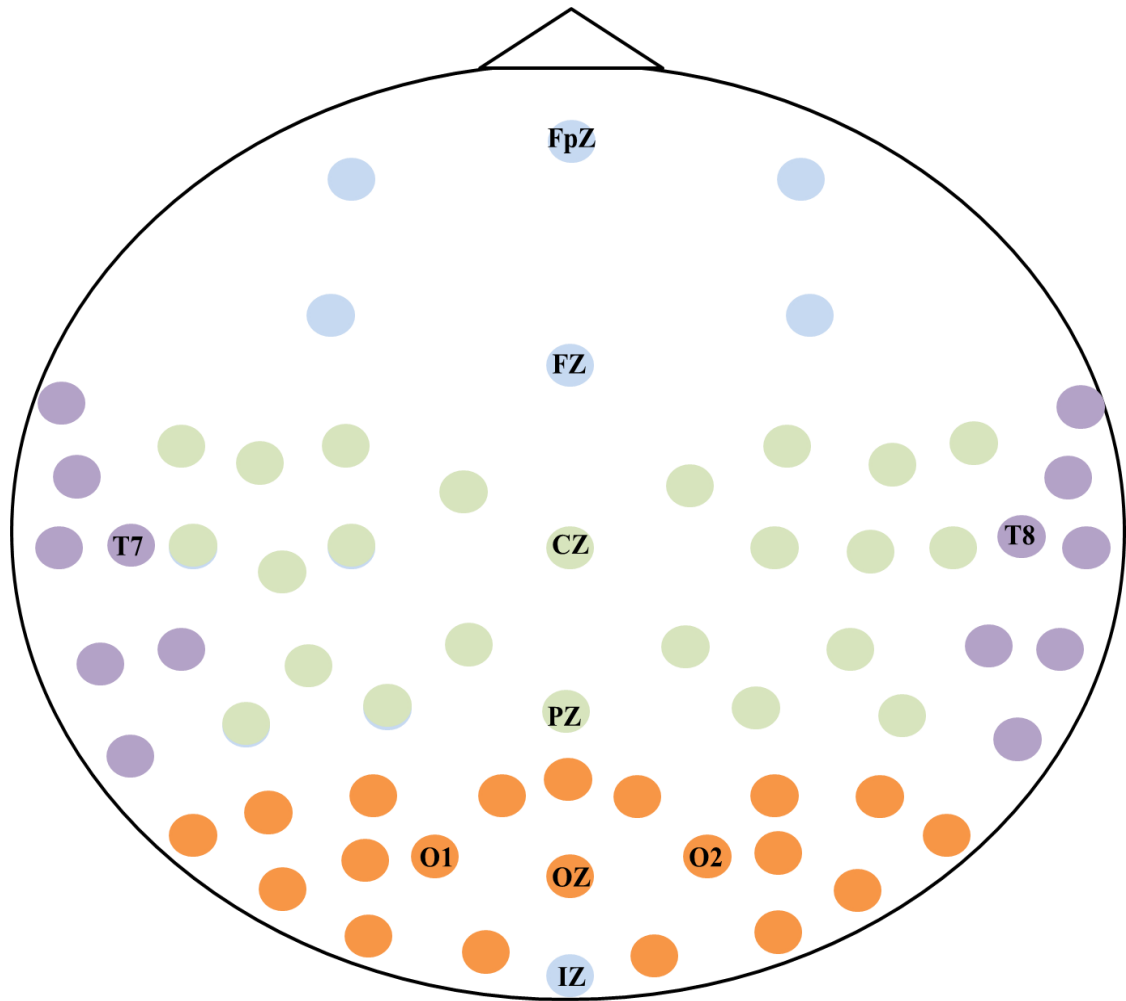


Figure 6.1, Schematic demonstration of the regions of interest examined in the transcranial magnetic current stimulation (TMS) evoked potential (TEP) analyses. Electrode locations were chosen based on their rough characterisation of the occipital (orange), parietal (green), and temporal (purple) cortices.

Mass-Univariate Analysis

In both groups the no-phosphene trial waveforms were averaged within their regions of interest and the amplitude at each time point compared between groups using the Mann-Whitney U test (significant at $p < .05$ using Fishers exact test). The family-wise error rate was controlled for using cluster temporal correction, e.g. a significant effect was considered if it lasted for at least 20ms (40 time points, using a sampling rate of 2048Hz; e.g. Taylor et al, 2010; Bagattini et al, 2015).

6.2.4 Statistical Analyses

Covariates

Because increasing field strength is associated with increased SI (Kommssi et al, 2004; Walsh & Pascual-Leone, 2003, ch.3) there was the possibility that the TEP component measurements could have been influenced more so by the SI than particular group membership. Therefore, despite a lack of differences between groups for the SI used and PT (see below), SI was further tested as a predictor of TEP measurements using the process described in **Chapter 3**. Due to the small sample sizes significant correlations from the phosphene trials were not tested with regression. For each component all correlations were corrected using the Bonferroni method for multiple comparisons ($\alpha = .016$).

Between Groups Comparisons

Stimulation Characteristics

The distributions of SI, PT, and PC values/scores were compared between groups using the Mann-Whitney U test. The frequencies of positive and negative responses were compared for an effect of group membership using the chi-squared test.

TMS Evoked Potentials

General Response

To avoid potentially mixing separate sources of activity the general response to TMS was measured from only trials in which phosphenes were not present. Measurements of each component were treated as separate entities and compared as such using 2x3 mixed analysis of variance (ANOVA; two levels of participant group (between groups factor), three levels of region (within group's factor)). Significant main effects and interactions were followed up using SPSS pairwise comparisons, Bonferroni corrected for multiple comparisons.

Phosphene Perception

Comparisons of the phosphene effect were performed using non-parametric tests. Within each group the Friedman test was used to estimate main effects of condition and region. Significant effects were followed up using Wilcoxon signed rank tests for pairwise comparisons, Bonferroni corrected for multiple comparisons ($\alpha = .016$). Since testing for more complicated interaction effects would result in an inflated error term the between groups phosphene effect was measured by comparing the percentage difference from each group for each region separately using the Mann Whitney U test, with the alpha value adjusted for multiple comparisons.

Within Groups Comparisons

Effect of Visual Hallucination Severity

In the PDD group all component measurements were tested for a relationship with VH severity (patient, NEVHI, and carer, NPI hallucinations subscale, ratings – see **Chapter 3**) using Spearman's correlations. Correlations were corrected for multiple comparisons, per component, using the Bonferroni method ($\alpha = .016$).

Stimulation Characteristics

Stimulation characteristics (SI, PT, and PC) within the PDD group were assessed for a relationship with the severity of VH, and CAF scores using Spearman's correlations. The influence of cholinesterase inhibitor (ChI) use was considered using point-biserial correlation. Analysis of trends from the point-biserial correlation was followed up by a comparison of the stimulation characteristics for those on versus off ChI using the Mann-Whitney U test. These investigations were performed to understand (if any) the relationship between these characteristics and disease related changes affecting the systems responsible for the control of visual attention (e.g. Bosboom et al, 2009; Perry et al, 1995; Taylor et al, 2011).

6.3 Results

6.3.1 Normality

Values for SI and PT were non-normally distributed in both groups, whilst PC scores for both groups were normally distributed. Measurements of the TEP components were normally distributed in both groups.

6.3.2 Covariates

The results of the covariate analyses are summarised in **Tables 6.2** (non-phosphene trials) & **6.3** (phosphene trials). In both groups the amplitudes and latencies of TEP components in non-phosphene trials was not significantly correlated with SI (except for the PDD temporal cortex component 2 amplitude, and the control component 4 latency [all ROI's]). In contrast phosphene trial TEP amplitudes for components one and two in both groups were positively correlated with SI when measured at the temporal ROI, additionally PDD temporal component three amplitudes were positively correlated with SI. Phosphene amplitudes from the parietal ROI were positively associated with SI at components one and three in the control participants, and at component two in the PDD group. Due to the increased potential for spurious correlations when using small sample sizes the results from the phosphene trial covariate analyses should be treated with caution. However overall, in the phosphene trials there was a suggestion that there was a generally positive association between SI and TEP component amplitude (especially earlier components). Nevertheless, given the less clear association between SI and TEP in the non-phosphene trials, SI was not used as a covariate in further analyses of the TEP.

Table 6.2, Covariate analyses, correlation between the general (no-phosphenes) transcranial magnetic current stimulation (TMS) evoked potential (TEP) amplitudes/latencies and stimulation intensity used during the TMS session. Significant correlations are highlighted in bold.

No-Phosphenes		Controls					PDD				
Region	Component	Amplitude		Latency			Amplitude			Latency	
		rs	<i>p</i> *	rs	β	<i>p</i> *	rs	β	<i>p</i> *	rs	<i>p</i> *
Occipital	<i>c1</i>	0.44	<i>0.1</i>	-0.12		<i>0.68</i>	0.32		<i>0.23</i>	0.44	<i>0.08</i>
	<i>c2</i>	0.38	<i>0.16</i>	-0.03		<i>0.92</i>	0.41		<i>0.11</i>	0.32	<i>0.23</i>
	<i>c3</i>	0.42	<i>0.12</i>	0.38		<i>0.16</i>	0.31		<i>0.24</i>	0.32	<i>0.23</i>
	<i>c4</i>	-0.38	<i>0.89</i>	0.64	3.004	0.02	0.29		<i>0.27</i>	0.17	<i>0.52</i>
Parietal	<i>c1</i>	0.48	<i>0.06</i>	-0.18		<i>0.53</i>	0.2		<i>0.47</i>	0.43	<i>0.1</i>
	<i>c2</i>	0.29	<i>0.3</i>	-0.05		<i>0.84</i>	0.47		<i>0.12</i>	0.36	<i>0.17</i>
	<i>c3</i>	0.43	<i>0.11</i>	0.41		<i>0.13</i>	0.36		<i>0.17</i>	0.31	<i>0.25</i>
	<i>c4</i>	0.25	<i>0.38</i>	0.65	3.01	0.02	0.27		<i>0.3</i>	0.16	<i>0.57</i>
Temporal	<i>c1</i>	0.31	<i>0.26</i>	-0.09		<i>0.75</i>	0.35		<i>0.19</i>	0.42	<i>0.11</i>
	<i>c2</i>	0.31	<i>0.26</i>	-0.02		<i>0.94</i>	0.52	0.03	0.04 †	0.39	<i>0.14</i>
	<i>c3</i>	0.37	<i>0.17</i>	0.41		<i>0.13</i>	0.34		<i>0.18</i>	0.31	<i>0.25</i>
	<i>c4</i>	0.04	<i>0.89</i>	0.65	3.1	0.02	0.14		<i>0.61</i>	0.15	<i>0.59</i>

* adjusted for multiple comparisons $\alpha = 0.016$

† Not significant when corrected for multiple comparisons

Significant correlations are highlighted in bold

Table 6.3, Covariate analyses, correlation between the phosphene transcranial magnetic current stimulation (TMS) evoked potential (TEP) amplitudes and stimulation intensity used during the TMS session. Correlations are highlighted in bold. Latencies are not included due to being identical to those in the general TEP condition.

Phosphenes		Controls		PDD	
Region	Component	Amplitude		Amplitude	
		rs	<i>p</i> *	rs	<i>p</i> *
Occipital	<i>c1</i>	0.63	0.067	0.62	0.08
	<i>c2</i>	0.6	0.08	0.79	0.01
	<i>c3</i>	0.78	0.01	0.69	0.04 †
	<i>c4</i>	0.45	0.22	0.59	0.09
Parietal	<i>c1</i>	0.8	0.01	0.62	0.07
	<i>c2</i>	0.67	0.05 †	0.83	0.006
	<i>c3</i>	0.77	0.01	0.61	0.08
	<i>c4</i>	0.67	0.05 †	0.52	0.15
Temporal	<i>c1</i>	0.83	0.005	0.79	0.01
	<i>c2</i>	0.78	0.01	0.87	0.002
	<i>c3</i>	0.88	0.002	0.83	0.006
	<i>c4</i>	0.35	0.35	0.48	0.18

* adjusted for multiple comparisons $\alpha = 0.016$

† Not significant when corrected for multiple comparisons

Significant correlations are highlighted in bold

6.3.3 Stimulation Characteristics

Phosphene frequencies and phenomenology are summarised in **Table 6.4**; tests of associations between PC scores and SI/PT are summarised in **Table 6.5**; tests of correlations between the stimulation characteristics and patient clinical variables are summarised in **Tables 6.6 & 6.7**.

Stimulation intensity (Controls, $mean = 71.3\% \pm 8.7\%$; PDD, $mean = 68.4\% \pm 13.9\%$) and PT (Controls, $mean = 83.5\% \pm 18.7\%$; PDD, $mean = 80.2\% \pm 23.1\%$) were not significantly different between groups (SI, $U = 184$, $Z = -.09$, $p = .95$; PT, $U = 117.5$, $Z = -.1$, $p = .93$). Likewise the frequency of phosphene responders was not significantly different between groups (*Partial and regular responders*, $\chi^2 = .1$, $CV = .016$, $p = .92$; *TEP analysis*, $\chi^2 = .045$, $CV = .038$, $p = 1$)¹. The complexity of the phosphenes reported by each group were not significantly different (Controls, $mean = 1.5 \pm 1.5$; PDD, $mean = 2.1 \pm 1.7$; $U = 167.5$, $Z = -.58$, $p = .585$), and correlated negatively with SI (see **Table 6.5**) when non-responders were included (with PTs assigned to be 101% of the stimulator output), although the strength of this correlation was reduced to non-significance when the sample was limited to responders only (see **Table 6.5**).

All participants who experienced phosphenes reported the presence of simple percepts, typically an amorphous blob or flash with no distinct shape. Less than half of the participants in each group reported seeing phosphenes that took on two dimensional shapes (see **Table 4**). In both groups two thirds of those reporting phosphenes described colours that were not grey, whilst less than half reported polychromatic or patterned sensations. Percept motion was reported in a third of cases within both groups. Finally, the experiences of more complex VH like phosphenes were described by three of the PDD participants, although by none of the control group. All three patients described images of people, and one participant also described images of a rocking horse. In one patient the people were described as having a conversation about football.

In both groups the reporting of phosphenes was observed with stimulation at the midline within 10% vertically of Oz, except in a single member of the control group in which stimulation was 2.6% laterally from electrode POz. The overall similarity of the phosphene

¹ In both groups the reported stimulation characteristics represent those who experienced phosphenes regularly (at least 50% of trials), and partially (less than 50% of trials). This is contrasted with a report of the stimulation characteristics for each group when only regular phosphene responders were included. These are referred to as the good TEP participants.

response profiles per group suggests that phosphene generation was not biased by group membership.

In the PDD group the stimulation characteristics were unrelated to the global decline in cognition, and fluctuations in attention. There were no relationships between the stimulation characteristics and either rating of VH severity. Furthermore, the use of cholinesterase inhibitors did not affect the stimulation profile (see **Table 6.7**).

Table 6.46 Comparison of phosphene responder frequency and phenomenology in both groups (including those whose transcranial magnetic current stimulation evoked potential [TEP] was not used in later analyses).

Group	Frequency of Phosphene Responders	Whole Sample	Characteristic (responders only)					
		Absent (%)	Simple (%)	2-D Geometric Shape (%)	Coloured (not grey) (%)	Polychromatic (%)	Motion (%)	VH Like (%)
<i>Controls</i>	9/17	47.06	9 (100)	3 (33.33)	6 (66.67)	3 (33.33)	3 (33.33)	0 (0)
<i>Controls (good TEP only)</i>	9/15	40.00	-	-	-	-	-	-
<i>PDD (all)</i>	12/21	42.86	12 (100)	5 (41.67)	8 (66.67)	5 (41.67)	4 (33.33)	3 (25)
<i>PDD (good TEP only)</i>	9/16	43.75	9 (100)	3 (33.33)	6 (66.67)	3 (33.33)	4 (44.44)	1 (11.11)

Table 6.5 Correlations between phosphene complexity and stimulation intensity/phosphene threshold, split to contrast the differences between the complete samples and the samples when only using phosphene responders. Significant correlations are highlighted in bold.

Phosphene Complexity	Spearman's Correlations (responders only)			
	Stimulation Intensity		Phosphene Threshold	
	rs	<i>p</i>	rs	<i>p</i>
<i>Controls</i>	-0.2	<i>0.62</i>	-	-
<i>PDD (all)</i>	-0.27	<i>0.39</i>	-	-
<i>PDD (good TEP only)</i>	-0.37	<i>0.33</i>	-	-
Spearman's Correlations (whole sample)				
<i>Controls</i>	-0.65	<.001	-0.87	<.001
<i>Controls (good TEP only)</i>	-0.62	<.001	-0.82	<.001
<i>PDD (all)</i>	-0.60	<.001	-0.85	<.001
<i>PDD (good TEP only)</i>	-0.61	0.013	-0.88	<.001

Table 6.6, Relationship between the PDD stimulation characteristics and clinical variables. The stimulation intensity refers to the percentage of the maximum machine output used per participant within the study. It should be noted that a potential factor underlying the lack of relationships between the stimulation intensity/Phosphene threshold and the clinical variables could be the arbitrary setting of the stimulation level for those who did not perceive phosphenes.

	Measurement											
	MMSE		CAMCOG (Total)		Cholinesterase Inhibitors		CAF		NPI Hallucinations		NEVHI	
	<i>rs</i>	<i>p</i>	<i>rs</i>	<i>p</i>	<i>rpb</i>	<i>p</i>	<i>rs</i>	<i>p</i>	<i>rs</i>	<i>p</i>	<i>rs</i>	<i>p</i>
Stimulation Intensity	-0.03	0.90	-0.07	0.77	-0.16	0.47	0.12	0.61	0.08	0.73	0.05	0.84
Phosphene Threshold	0.13	0.58	0.01	0.98	-0.29	0.20	-0.08	0.74	-0.22	0.33	-0.18	0.42
Phosphene Complexity	-0.67	0.77	0.002	0.99	0.28	0.22	0.31	0.17	0.36	0.11	0.37	0.09

*Taken from all participants who took part in the TMS session regardless of TEP quality (n = 21)

Table 6.7, Comparison of the stimulation characteristics for those taking vs not taking cholinesterase inhibitors.

	<i>Mann-Whitney U</i>								
	Stimulation Intensity			Phosphene Threshold			Phosphene Complexity		
	<i>MWU</i>	<i>p</i>	<i>r</i>	<i>MWU</i>	<i>p</i>	<i>r</i>	<i>MWU</i>	<i>p</i>	<i>r</i>
ChI vs No ChI	50.50	0.49	-0.15	39.50	0.15	-0.31	46.50	0.37	-0.20

6.3.4 TMS Evoked Potential – Window Method

Waveform and Windowing

The mean parameters for the windows used to measure the TEP components are summarised in **Table 6.8**, and visualised in **Figure 6.2**. The individual GFP derived measurement windows for each participant are listed in **Appendix 4**. In the GFP analyses both groups demonstrated a similar topography and temporal pattern. In both groups the first peak occurred between ~40ms and ~70ms, characterised by a fronto-central positivity and a posterior negativity. This was followed by a posteriolateral positivity coupled with a fronto-central negativity between ~90ms and ~150ms. The third peak occurred between ~150ms and ~230ms, appearing as a central positivity and a posterior negativity. The final peak was associated with a posterior positivity and a central negativity between ~225ms and ~330ms.

Table 6.8, The average latency of the group global field power windows estimated for each component. A list of the individual windows used can be found in Appendix.

	Peak (ms)	SD (+/-)	Confidence Interval (95%)	
			Lower	Upper
<i>Controls</i>				
<i>Component 1</i>	56.78	16.80	48.55	65.02
<i>Component 2</i>	111.23	17.29	102.75	119.70
<i>Component 3</i>	184.44	26.77	171.32	197.56
<i>Component 4</i>	269.98	45.13	247.87	292.09
<i>PDD</i>				
<i>Component 1</i>	61.97	20.78	52.37	71.58
<i>Component 2</i>	120.11	28.33	107.02	133.20
<i>Component 3</i>	194.49	33.47	179.03	209.95
<i>Component 4</i>	289.27	40.60	270.51	308.03

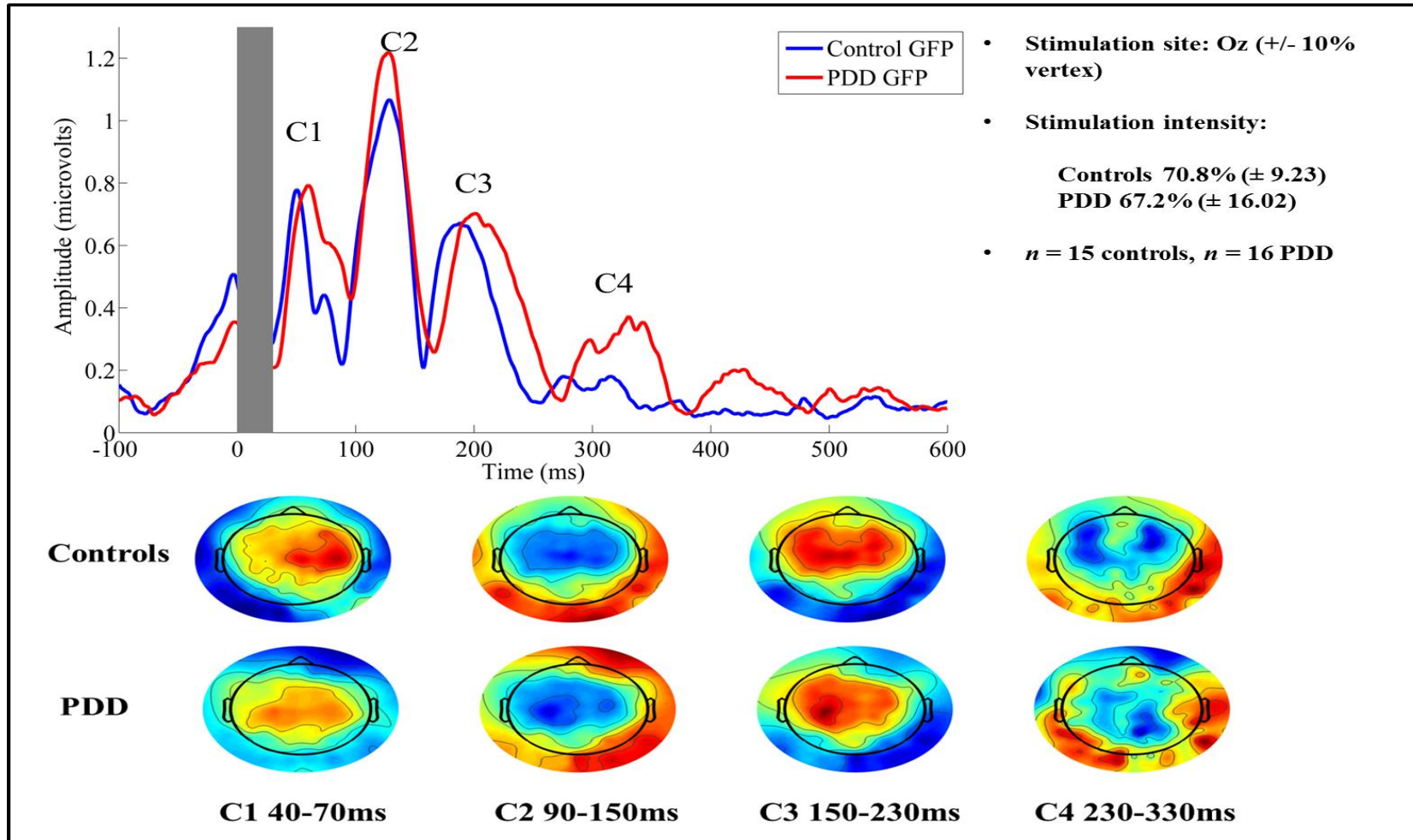


Figure 6.2, Comparison of group global field power maxima. The grey bar represents the time period which was replaced by interpolation (top); and their spatial distribution using topographic maps (bottom).

6.3.5 General TMS Evoked Potentials

The mean amplitude and latency values per group, for each component and region, are summarised in **Table 6.9**. It is notable that the latency values differ from those displayed in the GFP summary (**Table 6.8**) due to how the GFP is estimated and the inter-channel variance resulting in peak latencies not all being positioned in the centre of the window. Between group comparisons and their follow-up pairwise comparisons are summarised in **Tables 6.10 & 6.11**, and visualised in **Figures 6.3, 6.4, & 6.5**.

There were no significant main effects of group or region for the comparison of component latencies, and no significant interactions. Component amplitudes were not significantly different between groups, but were significantly different between regions. This was supported by moderate effect sizes for each component (partial eta squared; c1 $\eta^2 = .29$; c2 $\eta^2 = .406$; c3 $\eta^2 = .416$; c4 $\eta^2 = .3$), with the effect of region accounting for up to 40% of the variability in the TEP measurements. Follow-up pairwise comparisons revealed that the amplitudes for each component were significantly greater at the occipital ROI than at the parietal and temporal ROIs. The parietal ROI was also consistently significantly reduced in comparison to the occipital and temporal ROIs.

6.3.6 Relationship with Visual Hallucination Severity

Correlations between component measurements and VH severity are summarised in **Table 6.12**. In the PDD group the carer and patient ratings of VH severity were positively correlated with the amplitudes of component three and component four at the temporal ROI. Trending relationships between the measurements of VH severity and component amplitudes were noted for components two (occipital ROI), three and four (occipital and parietal ROI). VH measures were, however, unrelated to measurements of component latency.

Table 6.9, Group mean amplitudes and latencies per region for each component.

	Region	Mean Amplitude (ms ±)		Mean Latency (µv ±)	
		Control	PDD	Control	PDD
<i>Component 1</i>	Occipital	1.76 (1.8)	1.5 (1.01)	56.8 (17.4)	59.4 (16.2)
	Parietal	1.1 (.94)	1.01 (.69)	56.8 (17.8)	59.5 (15.9)
	Temporal	1.32 (.84)	1.09 (.61)	56.95 (18.2)	60.52 (16.7)
<i>Component 2</i>	Occipital	1.88 (1.4)	1.95 (1.3)	115.98 (21.6)	116.86 (20.2)
	Parietal	1.17 (.78)	1.35 (.89)	114.25 (20.4)	116.2 (20.4)
	Temporal	1.46 (.64)	1.54 (.93)	114.5 (19.1)	115.5 (19.6)
<i>Component 3</i>	Occipital	1.4 (.96)	1.33 (1.14)	186.24 (28.8)	187.98 (26.2)
	Parietal	.85 (.65)	.88 (.76)	185.74 (27.8)	187.9 (24.1)
	Temporal	1.05 (.58)	.99 (.74)	186.4 (26.6)	186.58 (24.3)
<i>Component 4</i>	Occipital	.63 (.5)	.77 (.55)	267.8 (47.1)	287.75 (40)
	Parietal	.26 (.3)	.48 (.3)	269.03 (47.5)	286.92 (40)
	Temporal	.53 (.27)	.58 (.34)	267.53 (48.5)	286.78 (40)

Table 6.10, Results of the repeated measures analysis of variance for the general transcranial magnetic stimulation evoked potential (TEP). Partial eta squared (η^2) was used as a measure of effect size. Significant effects are highlighted in bold.

	Amplitude			Latency		
	F	<i>p</i> *	η^2	F	<i>p</i> *	η^2
<i>Group</i>						
Component 1	0.297	0.59	0.01	0.23	0.64	0.008
Component 2	0.099	0.76	0.003	0.03	0.86	0.001
Component 3	0.014	0.91	<.001	0.02	0.89	0.001
Component 4	0.37	0.55	0.013	1.45	0.24	0.048
<i>Region</i>						
Component 1	11.82	0.001	0.29	0.67	0.51	0.023
Component 2	19.84	<.001	0.41	2.79	0.07	0.09
Component 3	20.65	<.001	0.416	0.68	0.49	0.023
Component 4	12.45	<.001	0.3	1.13	0.33	0.037
<i>Region*Group</i>						
Component 1	2.6	0.68	0.009	0.54	0.59	0.018
Component 2	0.16	0.77	0.006	0.39	0.68	0.013
Component 3	0.21	0.79	0.007	2.17	0.13	0.07
Component 4	0.47	0.59	0.016	1.54	0.22	0.05

* adjustment for multiple comparisons $\alpha = 0.012$

Table 6.11, Pairwise comparisons for the main effect of region during the measurement of general transcranial magnetic stimulation evoked potential (TEP) amplitude. Significant effects are highlighted in bold. Confidence interval was estimated at 95%.

	Pairwise Comparison (Amplitude)	Mean difference	p	CI
<i>Component 1</i>	Occipital - Parietal	0.578	<.001	.24 : .92
	Occipital - Temporal	0.424	0.032	.03 : .82
	Parietal - Temporal	-0.154	0.053	-.31 : .001
<i>Component 2</i>	Occipital - Parietal	0.66	<.001	.373 : .95
	Occipital - Temporal	0.42	0.011	.08 : .75
	Parietal - Temporal	-0.24	<.001	-.39 : -.09
<i>Component 3</i>	Occipital - Parietal	0.49	<.001	.29 : .7
	Occipital - Temporal	0.34	0.003	.11 : .58
	Parietal - Temporal	-0.15	0.051	-.31 : 0
<i>Component 4</i>	Occipital - Parietal	0.25	<.001	.11 : .38
	Occipital - Temporal	0.15	0.056	-.003 : .3
	Parietal - Temporal	-0.1	0.021	-.18 : .01

Table 6.12, Correlations between regional component measurements of amplitude/latency and visual hallucination (VH) severity (NPI, carer; NEVHI, patient). Abbreviations: NPI – Neuropsychiatric Inventory (hallucinations subscale); NEVHI – North East Visual Hallucinations Interview.

Amplitude	Region	NPI Hallucinations				NEVHI			
		Amplitude		Latency		Amplitude		Latency	
		<i>rs</i>	<i>p</i> *	<i>rs</i>	<i>p</i> *	<i>rs</i>	<i>p</i> *	<i>rs</i>	<i>p</i> *
<i>Component 1</i>	Occipital	0.37	0.15	0.26	0.33	0.34	0.19	0.18	0.50
	Parietal	0.34	0.19	0.34	0.20	0.32	0.23	0.26	0.33
	Temporal	0.36	0.17	0.34	0.19	0.34	0.20	0.28	0.29
<i>Component 2</i>	Occipital	0.54	0.03	0.45	0.08	0.52	0.04	0.40	0.13
	Parietal	0.41	0.12	0.38	0.14	0.37	0.16	0.32	0.22
	Temporal	0.40	0.13	0.40	0.12	0.38	0.14	0.35	0.19
<i>Component 3</i>	Occipital	0.57	0.02	0.10	0.71	0.55	0.03	0.09	0.74
	Parietal	0.53	0.03	0.08	0.78	0.51	0.04	0.06	0.82
	Temporal	0.66	0.01	0.07	0.81	0.61	0.01	0.04	0.87
<i>Component 4</i>	Occipital	0.55	0.03	0.32	0.23	0.50	0.05	0.28	0.29
	Parietal	0.43	0.09	0.33	0.21	0.39	0.13	0.30	0.26
	Temporal	0.71	0.00	0.32	0.23	0.69	0.00	0.28	0.29

* adjusted for multiple comparisons $\alpha = 0.016$

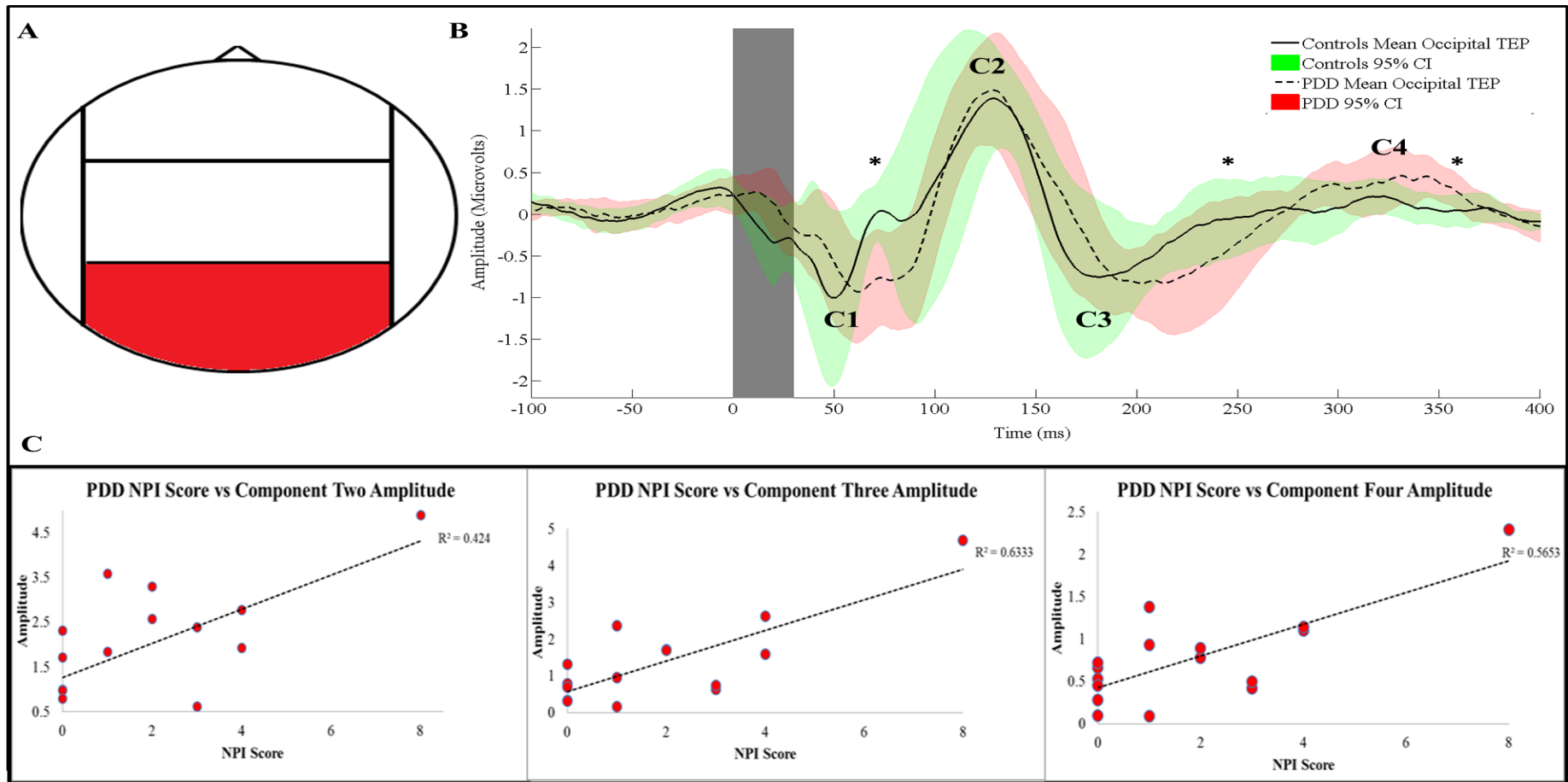


Figure 6.3, A) schematic of the occipital region of interest. B) Mean group transcranial magnetic stimulation evoked potentials (TEPs) from the general condition (no-phosphenes) with 95% confidence Intervals. The grey bar represents the time period which was replaced by interpolation. Asterisks represent intermittent periods of interest. C) Correlations between visual hallucination (VH) severity and component (2, 3 & 4) amplitudes.

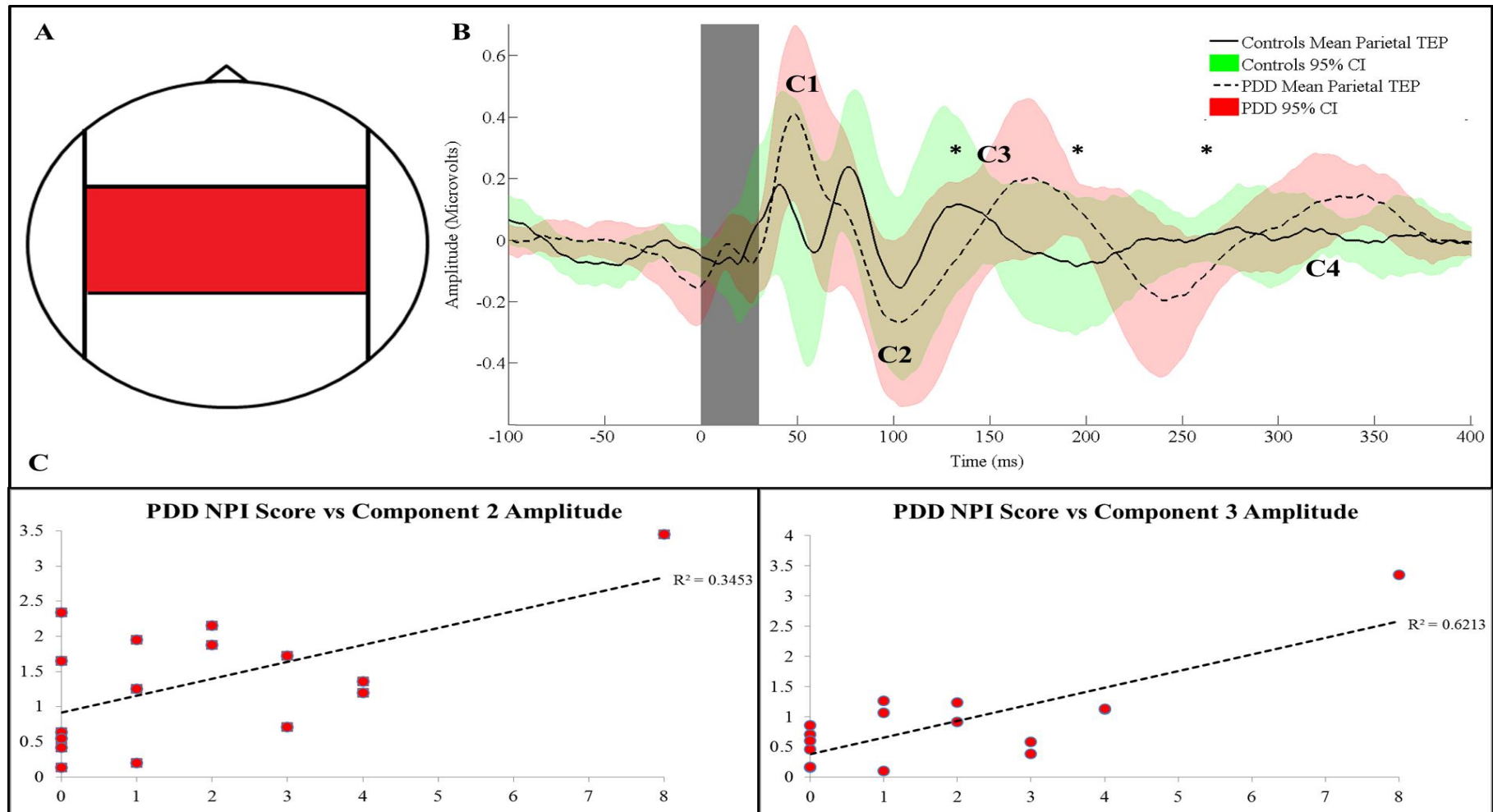


Figure 6.4, A) schematic of the parietal region of interest. **B)** Mean group transcranial magnetic stimulation evoked potentials (TEPs) from the general condition (no-phosphenes) with 95% confidence Intervals. The grey bar represents the time period which was replaced by interpolation. Asterisks represent intermittent periods of interest. **C)** Correlations between visual hallucination (VH) severity and component (2 & 3) amplitudes.

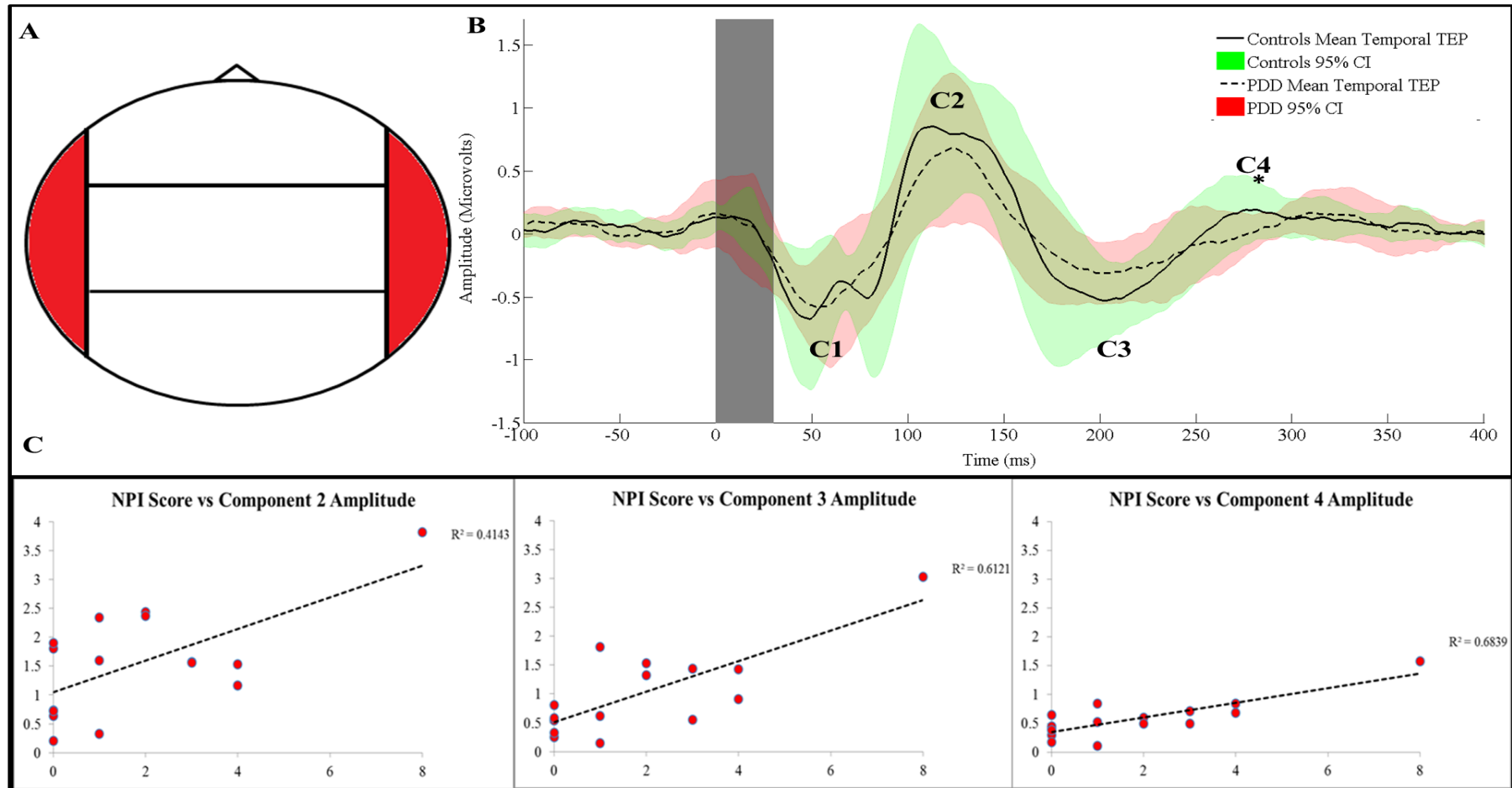


Figure 6.5, A) schematic of the temporal region of interest. **B)** Mean group transcranial magnetic stimulation evoked potentials (TEPs) from the general condition (no-phosphenes) with 95% confidence Intervals. The grey bar represents the time period which was replaced by interpolation. Asterisks represent intermittent periods of interest. **C)** Correlations between visual hallucination (VH) severity and component (2, 3 & 4) amplitudes.

6.3.7 Phosphenes Perception

Neither group demonstrated significant modulation of their TEP component amplitudes in response to phosphenes perception (all $p > .05$; **Figures 6.6, 6.7 & 6.8, Table 6.13**). Follow up between groups comparisons revealed that the percentage difference between conditions was also not significantly different between groups (all $p > .05$).

Table 6.137, Comparison of the regional component amplitudes between the no-phosphene and phosphene trials in each participant group. The percentage differences for each group were compared to provide an insight into the similarity in terms of component amplitude modulation in response to phosphene perception.

Amplitude	Region	<i>Amplitude Difference (NPH - PH)</i>						
		Controls			PDD			Phosphene Effect Between Groups
		<i>Uv</i>	<i>% difference</i>	<i>p</i> *	<i>Uv</i>	<i>% difference</i>	<i>p</i> *	<i>p</i> *
<i>Component 1</i>	Occipital	-0.17	-14.76	0.20	0.24	12.95	0.04	0.02
	Parietal	-0.05	-4.40	0.57	0.03	3.18	0.65	0.44
	Temporal	-0.11	-9.41	0.25	0.01	1.95	0.57	0.34
<i>Component 2</i>	Occipital	-0.01	-15.84	0.43	0.21	5.46	0.43	0.27
	Parietal	0.05	6.43	0.57	0.12	1.34	0.43	0.76
	Temporal	0.07	4.49	0.65	0.12	-1.25	0.43	0.90
<i>Component 3</i>	Occipital	0.06	-4.37	1.00	0.10	-0.22	0.25	0.49
	Parietal	-0.01	-9.89	0.73	0.01	-11.16	0.30	0.61
	Temporal	0.05	0.18	0.43	0.03	-13.64	0.73	0.86
<i>Component 4</i>	Occipital	-0.01	-20.17	0.82	0.00	-12.67	1.00	0.55
	Parietal	-0.01	-18.10	0.91	-0.09	-23.71	0.91	0.93
	Temporal	-0.08	-31.86	0.65	-0.11	-14.89	0.65	0.86

* adjusted for multiple comparisons $\alpha = 0.016$

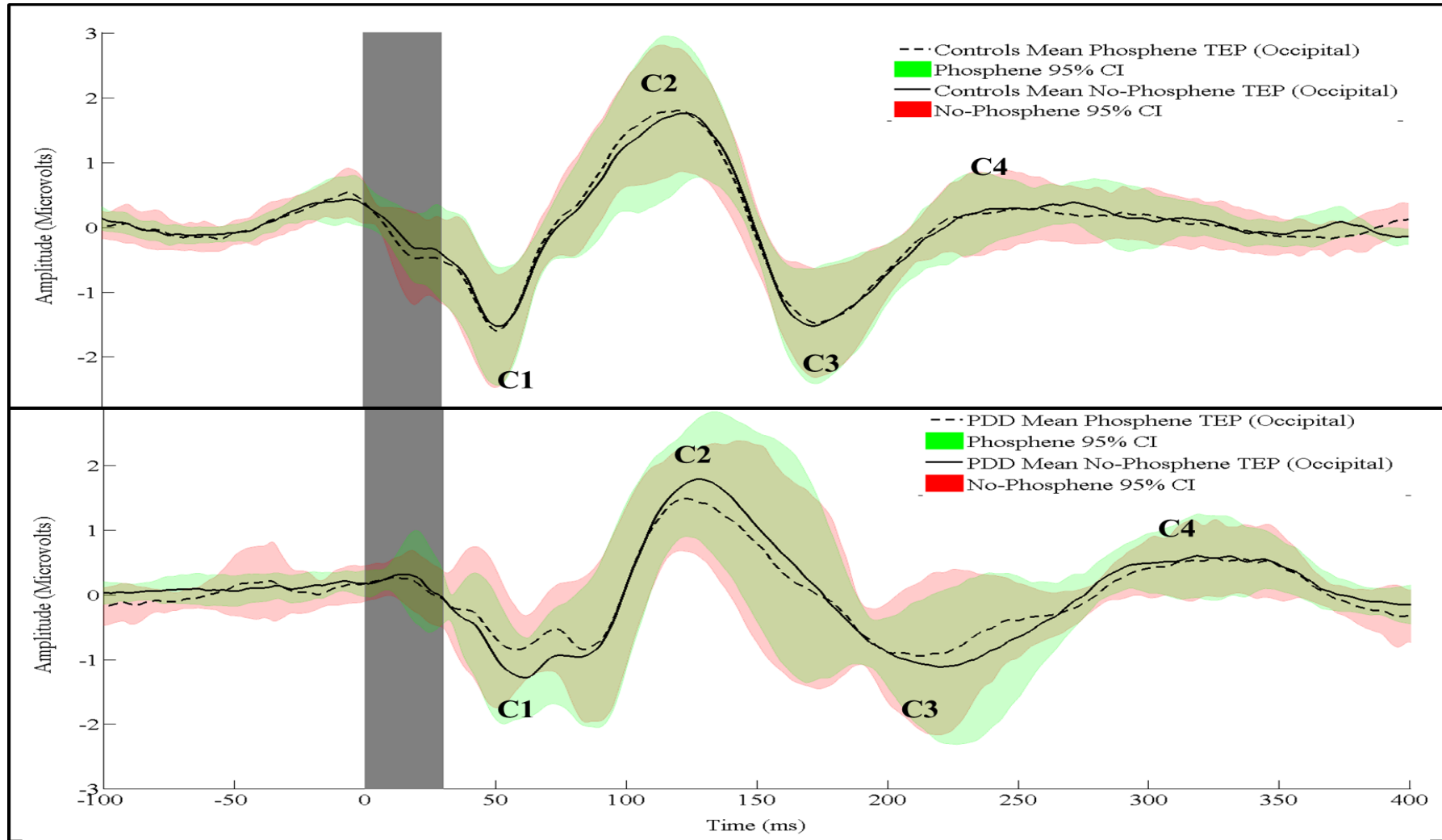


Figure 6.6, Comparison of phosphene versus no-phosphene occipital waveforms between the control (top) and PDD (bottom) groups.

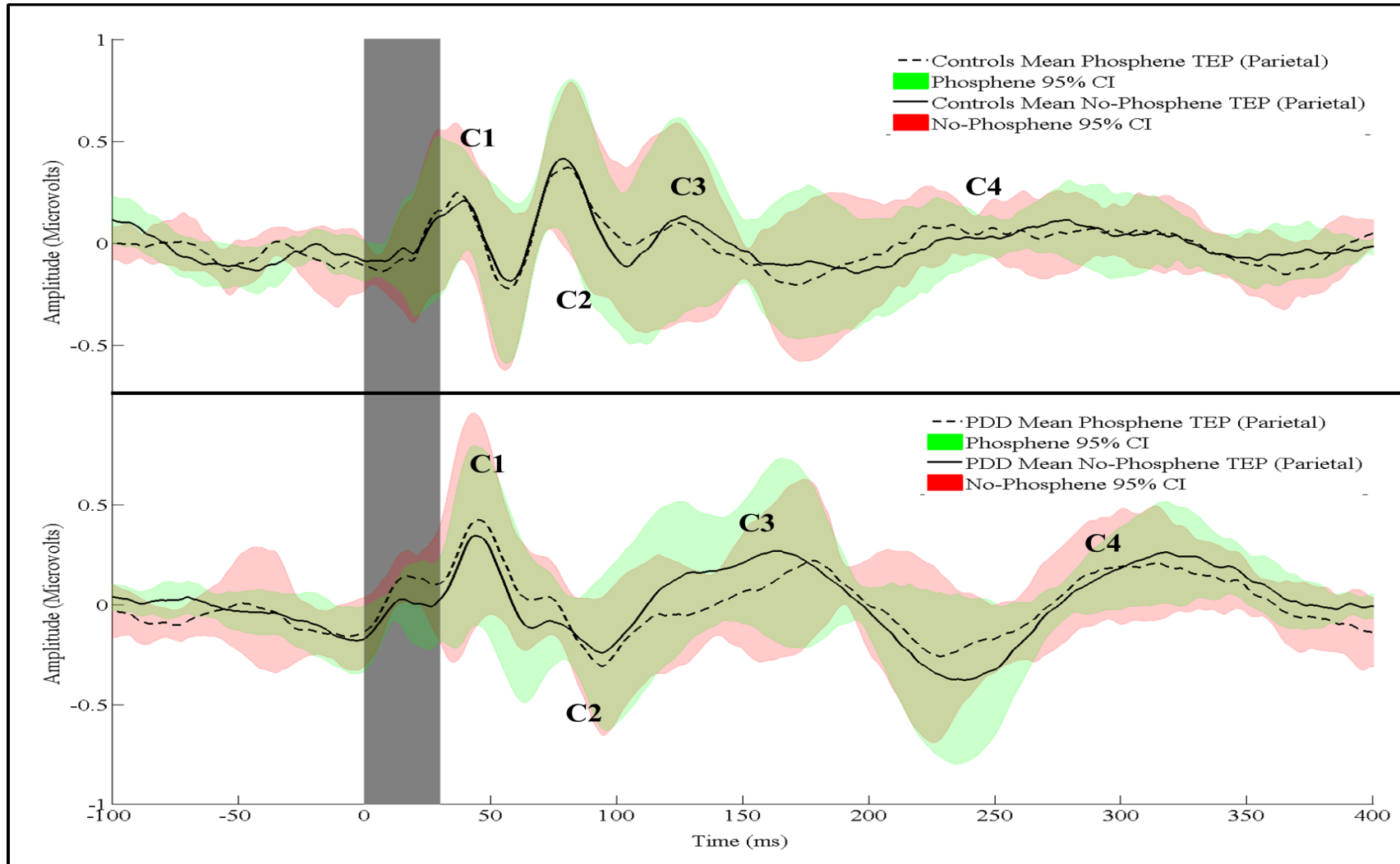


Figure 6.7, Comparison of phosphene versus no-phosphene parietal waveforms between the control (top) and PDD (bottom) groups.

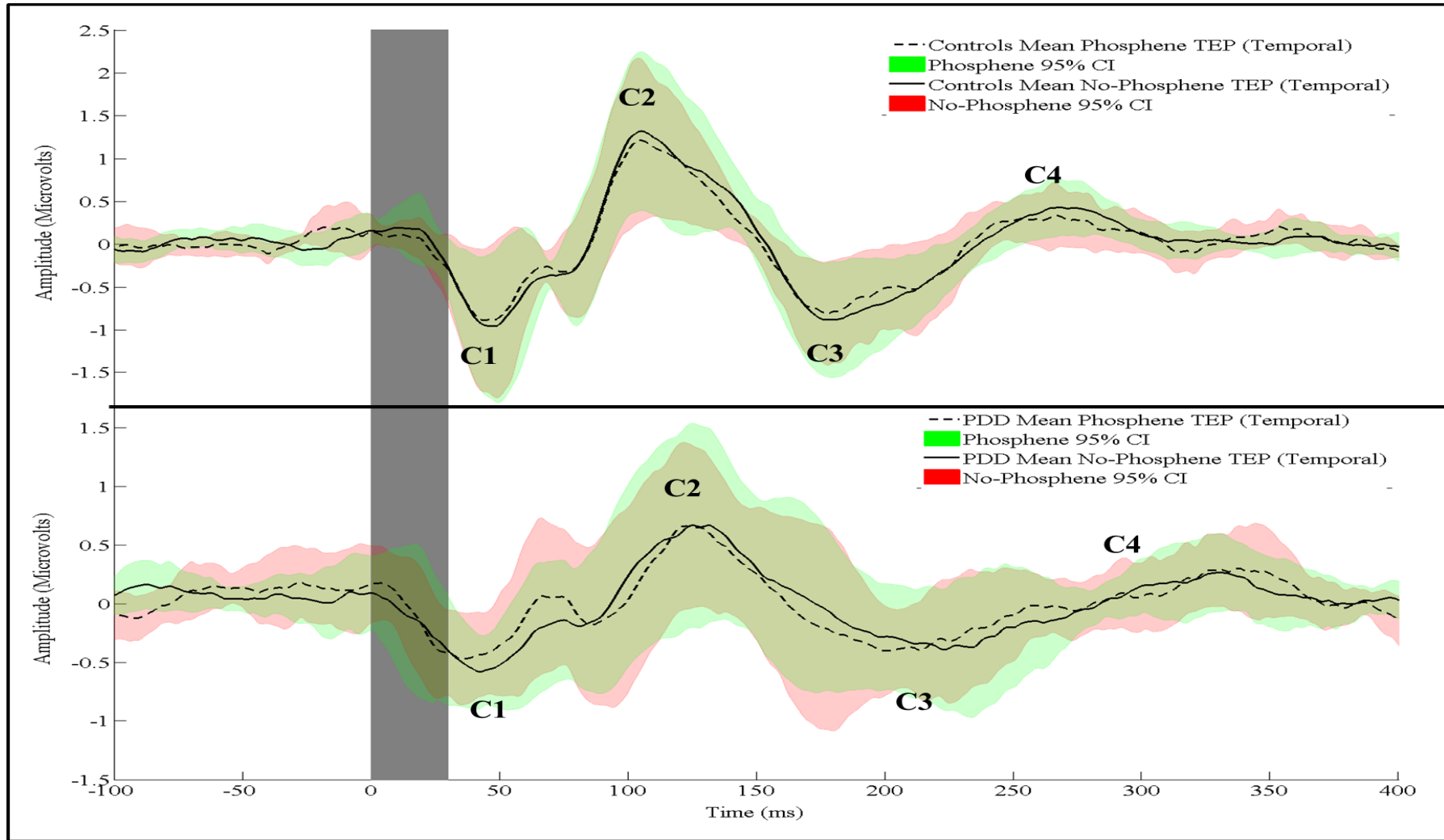


Figure 6.8, Comparison of phosphene versus no-phosphene temporal waveforms between the control (top) and PDD (bottom) groups.

6.3.8 TMS Evoked Potential – Mass Univariate Method

Cluster timings, sizes, and *p* values are summarised in **Table 6.14** and visualised in **Figures 6.9, 6.10 & 6.11**.

Occipital ROI

Two periods of divergent activity were discovered at the occipital ROI between 66ms and 92ms, and between 339ms and 353ms, however only the early cluster met the criterion of a minimum 20ms consecutive effect. Within both periods of activity the amplitude of the control waveform was significantly greater than the control waveforms.

Parietal ROI

There were three periods of differential activity at the parietal ROI: 181ms to 202ms, 447 to 465ms, and 517ms to 531ms. However, only the first period satisfied the criterion for a significant effect. During the first two periods the PDD amplitude was greater than the control group amplitude, but was less than the control group in the final period.

Temporal ROI

A single significant effect was demonstrated at the temporal ROI between 437ms and 468ms during which the PDD amplitude was significantly less than the control amplitude.

Relationship with VH

In the PDD group the average amplitudes across each period did not show any relationship with carer or patient measures of VH severity at any of the ROIs (see **Table 6.14**).

Table 6.14, Latency information for clusters of significant between groups differences during the mass univariate analyses. Significant clusters with at least 20ms duration are highlighted in bold.

Region	Cluster #	Start (ms)	End (ms)	Duration (ms)	Reject Null?	NPI		NEVHI	
						Hallucinations		<i>rs</i>	<i>p</i>
<i>Occipital</i>									
	1	66.41	91.31	24.90	Yes	-0.2	0.44	-0.19	0.47
	2	339.35	353.52	14.17	No	-0.3	0.36	-0.26	0.34
<i>Parietal</i>									
	1	181.64	201.66	20.02	Yes	-0.1	0.6	-0.21	0.43
	2	447.75	465.33	17.58	No	0.09	0.73	0.11	0.68
	3	517.10	531.25	14.15	No	-0.2	0.56	-0.13	0.64
<i>Temporal</i>									
	1	437.01	468.26	31.25	Yes	-0	0.91	0.02	0.95

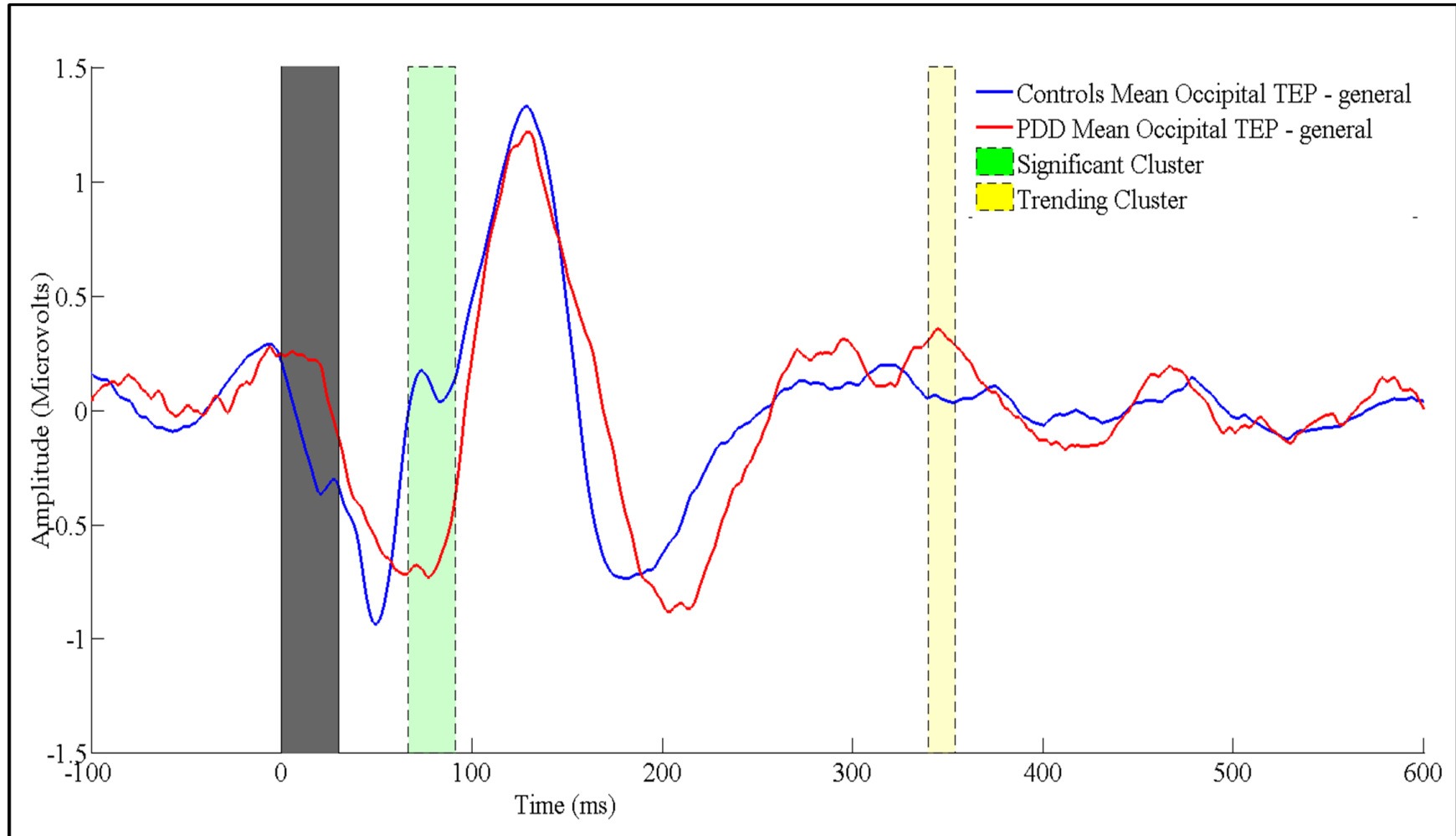


Figure 6.9, mass univariate comparison of the control and PDD mean occipital transcranial magnetic stimulation evoked potentials (TEPs). The grey rectangle represents the period replaced by interpolation. The green rectangle represents a significant cluster of differences. The yellow rectangle represents a notable but not significant cluster of differences.

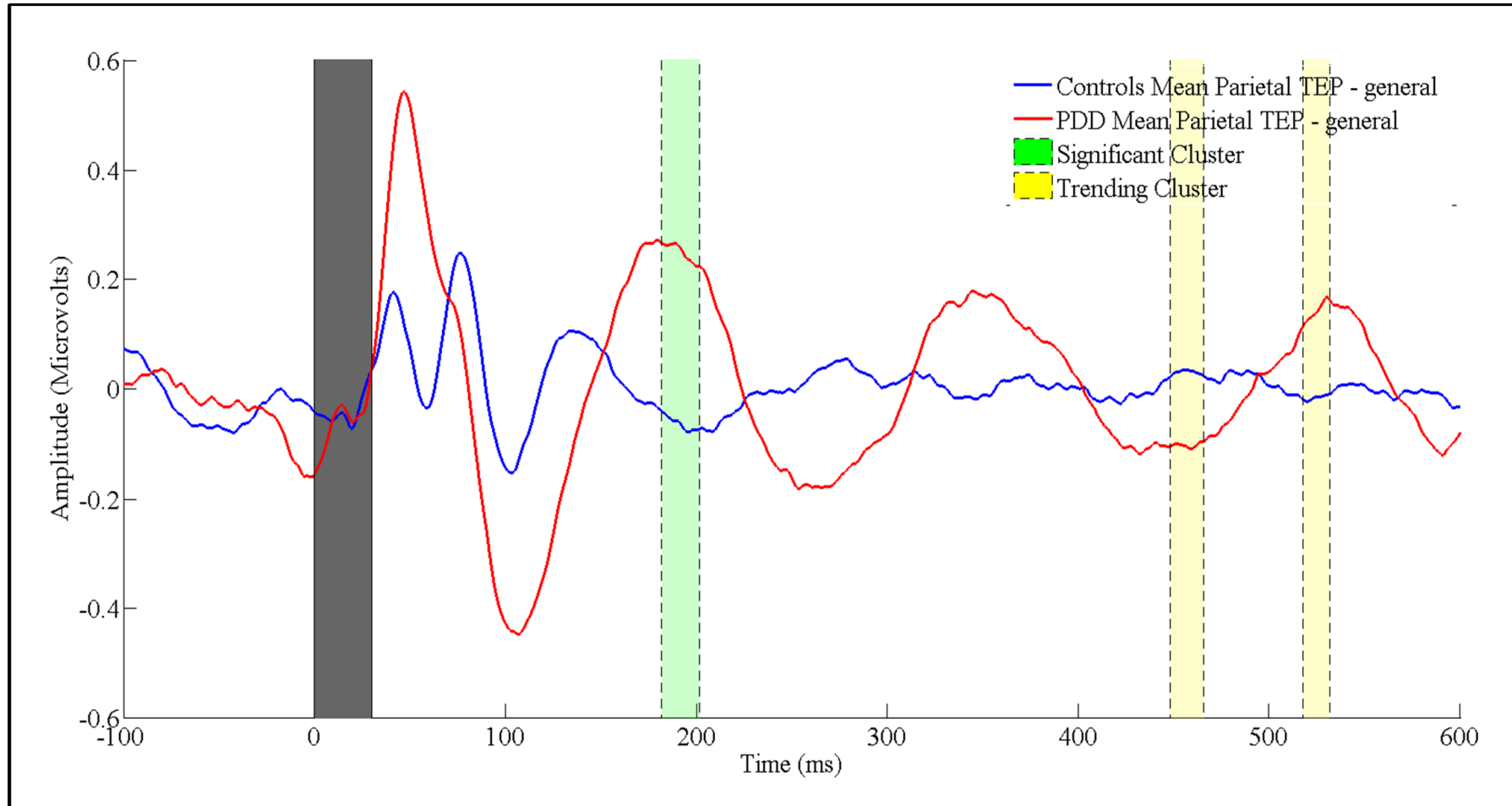


Figure 6.10, mass univariate comparison of the control and PDD mean parietal transcranial magnetic stimulation evoked potentials (TEPs). The grey rectangle represents the period replaced by interpolation. The green rectangle represents a significant cluster of differences. The yellow rectangles represent notable but not significant clusters of differences.

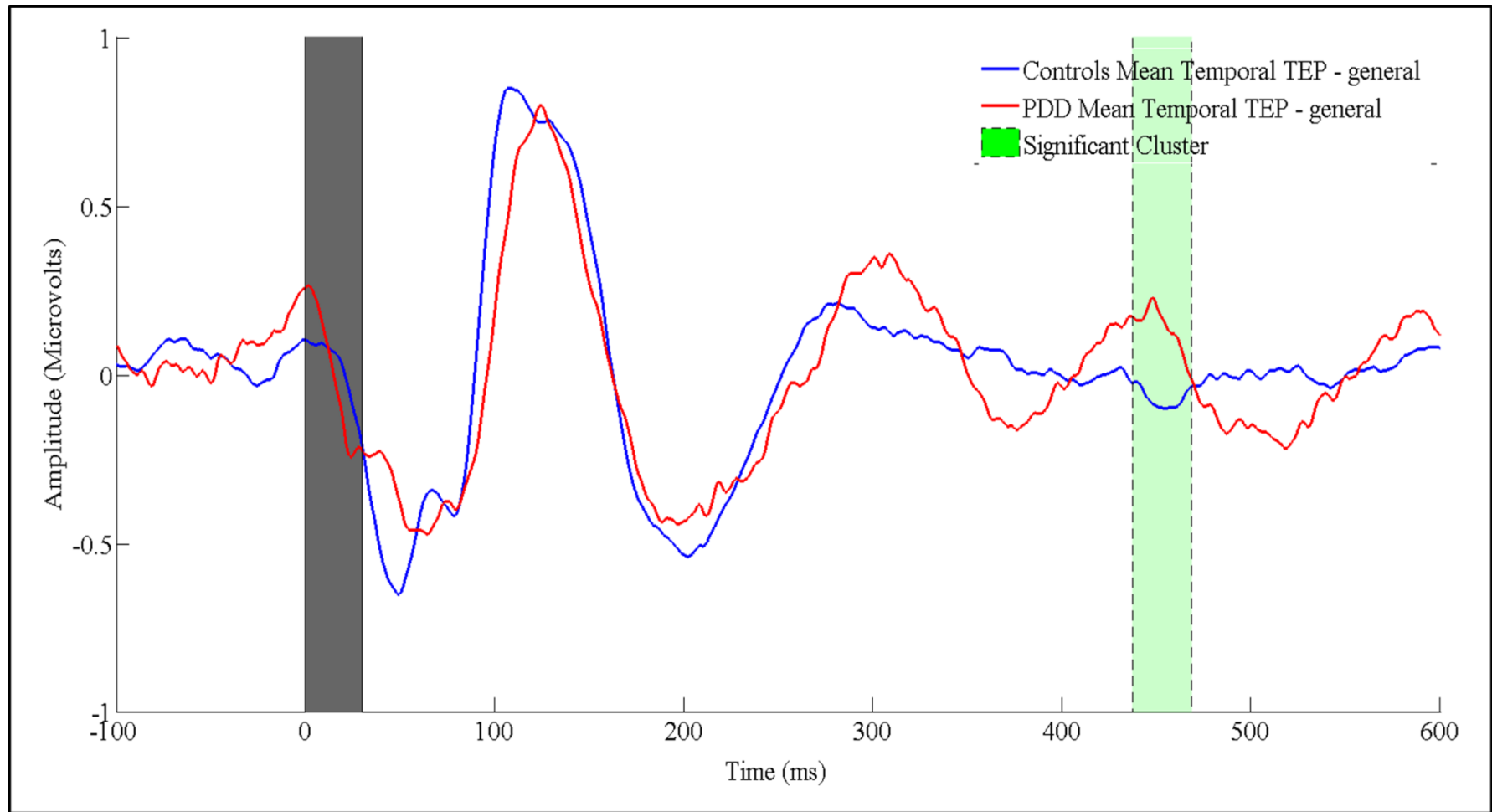


Figure 6.11, mass univariate comparison of the control and PDD mean temporal transcranial magnetic stimulation evoked potentials (TEPs). The grey rectangle represents the period replaced by interpolation. The green rectangle represents a significant cluster of differences.

6.4 Discussion

In this study TMS was applied to the occipital cortex during concurrent EEG to study the spatio-temporal and phenomenological response to stimulation in those with PDD and contrasted with the responses of a healthy age matched control group. The investigation revealed that although both groups shared a similar response profile the correlates of synaptic communication (evoked activity) demonstrated an altered pattern of behaviour in the PDD group relative to the control group. The implications of this for understanding PDD related physiological changes in the bottom-up stream of processing are discussed in more detail below.

6.4.1 TMS Evoked Potentials

The application of TMS depolarises axons of underlying neurons (aligned perpendicular to the coil) and generates a string of activity across a network of functionally connected regions (Garcia et al, 2011; Paus et al, 1997). The simplest method for observing the resulting communication during concurrent EEG is the TMS evoked potential, which represents the evoked pattern of synaptic activity in response to stimulation. In both groups the GFP estimates displayed four peaks relating to prominent activity between 40 and 330ms, similar to the profiles shown in previous studies done with healthy controls using a similar stimulation site (Taylor et al, 2010; Herring et al, 2015; Garcia et al, 2011; Bagattini et al, 2015). The windowing method of TEP measurement revealed that whilst the component amplitudes and latencies (at each component) do not perfectly match up there were no significant differences in the peak measurements between the two groups (across all regions). Based on this outcome it could be tempting to conclude that the bottom-up stream of processing, in terms of synaptic potential generation, remains intact in PDD. However, in actual fact the cortical response to stimulation is much more complex than it would appear from observation of the TEP. For example, Garcia and colleagues (Garcia et al, 2011) demonstrated that occipital cortex stimulation evoked activity across a network of frequency dependent connections (predominantly in the alpha and theta bands) that existed for several hundreds of milliseconds over a wide range of sites. When taking this into consideration it can be argued that a complete picture of PDD visual system physiology cannot be obtained from simply observing activity within a brief temporal window. Despite the implications of this caveat it does not discount that at some level there are similarities in the cortical response along the bottom-up pathways, even at later components (which might be thought of as being more directly implicated in top-down mediated feedback loops, previously assumed to be

disrupted in LBD, e.g. Kurita et al, 2010), suggesting that the populations of neurons contributing to these components are not intrinsically dysfunctional.

Due to the pitfalls associated with the windowing method we chose to expand the analyses by including a simplified variant of the mass-univariate approach to time series comparisons that has previously been implemented in concurrent TMS-EEG studies (Bagattini et al, 2015; Taylor et al, 2010), and is gaining acceptance in the wider case of M/EEG analyses (Maris & Oostenveld, 2007; Mensen & Khatami, 2013; Groppe et al, 2011). When appropriately controlling for family-wise error rate this method provides a more data driven, empirical approach to hypothesis testing, and importantly can test temporal and spatial properties of the response that are smoothed over in more traditional methods. In the current study the spatial resolution of the data was sacrificed to improve the signal to noise ratio of the waveforms in each group, and to reduce the likelihood of false positives. Its successful application highlights a point for future work in which the method should be applied at the individual channel level and contrasted with the current findings.

Across all regions of interest the PDD group waveforms exhibited periods of activity during which the pattern of the response was different from the control group (see **Figures 6.9, 6.10 & 6.11**). This was supported by the finding of regionally distinct patterns of altered amplitude-latency pairings to suggest that there is a slowing of the EEG response in the PDD group. Garcia and colleagues (2011) demonstrated that the cortical response to TMS was characterised by a predominantly slow wave response consisting of theta and alpha rhythm contributions. Based on this it is possible that these changes might stem from the global reduction in alpha power and subsequent increase in theta power demonstrated in PDD patients (Bosboom et al, 2006; Stoffers et al, 2007; Bosboom et al, 2009; Pugnetti et al, 2010), thought to arise from cholinergic deafferentation and the lesioning of several neurotransmitter systems projecting from the brainstem (*Noradrenergic, dopaminergic, serotonergic*; Berridge et al, 1993; Vanderwolf & Baker, 1986; Kropf & Kuschinsky, 1991; Babiloni et al, 2011; Berridge et al, 1993; Vanderwolf et al, 1990; Bosboom et al, 2006). At a physiological level this results in the slowing of the peak alpha rhythm, often into a high theta rhythm (see discussion in **Chapter 7**; Bonanni et al, 2008), with the functional consequences of these oscillatory changes being an impoverished control of attention and reduced neuronal gain (Chaumon et al, 2014; Rajagovindan et al, 2011). Thus it is possible that the promotion of increased slow wave contributions might result in an extended phase of the TMS evoked potential. However, to better understand this phenomenon the waveforms should be decomposed using wavelet analysis and their spectral content compared over time relative to

the control group. Alternatively the apparent slowing of the EEG response might be related to the deposition of alpha synuclein at the pre-synapse promoting inefficiency of synaptic communication through dendritic loss (e.g. Schulz-Schaeffer, 2010). This would suggest that changes in the waveform arise from purely bottom-up disruption caused by the spread of pathology, rather than from dysfunctional top-down control of neural excitability. Against this, is the relative sparing of early visual areas in terms of alpha-synuclein deposition (Morris et al, 2015) although pathology builds significantly with anterior progression along the ventral stream (Dey et al, 2015). Further, as previously discussed LBDs have been associated with altered gamma-aminobutyric acid (GABA) neuron communication, acting to disrupt the normal pattern of interneuronal inhibition (e.g. Morris et al, 2015). Based on the existing functional, structural, and post-mortem literature it is clear that the efficiency of local and long distance communication is reduced (Peraza et al., 2015; Cromarty et al, 2016; Dauwan et al, 2016), however, as previously stated, without the appropriate data it is not possible to form a solid conclusion of what is causing the EEG changes.

Despite being unable to conclude on the physical basis of these changes the timings of the differences provide an insight into their possible functional basis. The key affected periods overlap with the timings of components previously shown to be modulated by visual attention at the occipito-parietal electrodes (Herring et al, 2015; Taylor et al, 2010; Baggatini et al, 2015), implying that synaptic communication might be affected in a functional sense rather than inherently. This is further supported by the realigning of the waveform phases around the peak of component two, which would continue to be out of phase if there was a generic slowing of all occipito-parietal synapses. The finding of between groups temporal differences at the parietal cortex further supports evidence of functional disconnections from other visual attention networks (Shine et al, 2014; Peraza et al, 2014), implying that the timing of activity might be a marker for the poor application of exogenous attention in LBD. However, whether these patterns represent a slowing in response to dysfunctional top-down influences or an inherent inefficiency along the visual stream in terms of feed-forwards and feedback communication is not clear. Irrespective of the direction of the effect these findings fit with earlier descriptions of physiological changes to the occipital cortex and the dorsal stream, such as hypometabolism (Colloby et al, 2002), reduced cortical activity in response to visual stimuli (Taylor et al., 2012), cortical thinning (Burton et al, 2004), and neurotransmitter deficiencies (Bosboom et al, 2006; Morris et al, 2015).

6.4.2 Stimulation, Phosphenes, and Phenomenology

When the strength of the TMS pulse is sufficient, stimulation over posterior visual regions can lead to the perception of an artificial experience of light known as a phosphene. Although the precise properties of phosphenes are often varied between individuals (Marg & Rudiak, 1994), the common principles such as colour, motion, and shapes can provide a crude measure of the propagation strength of the TMS pulse through the visual system (e.g. Taylor et al, 2011). Moreover the threshold at which visual detection of phosphenes becomes possible provides a simple measure of cortical excitability (e.g. Kammer et al, 2001), and thus a correlate of the control of visual attention and information flow. Although the source of phosphene generation has been the focus of much research (e.g. Rule et al, 2011; Kammer et al, 2001; Taylor et al, 2010; Bagattini et al, 2015; Caparelli et al, 2010), there is still no consensus on a complete mechanism.

In this study both groups had similar numbers of phosphene responders, and both groups shared similar stimulation profiles (phosphene threshold, complexity, and stimulation location). The combination of results highlights the possibility that the mechanisms generating the phosphenes are the same in both groups, and further that the functional integrity of basic visual processing in the cortex is not compromised by the presence of Lewy body pathology.

Similar findings were recently reported in a dementia with Lewy bodies population (DLB; Taylor et al, 2011), demonstrating that the patterns of visual cortex excitability overlap between controls and DLB. In the present study and that by Taylor et al. (2011) all participant groups demonstrated an increase in phosphene complexity associated with a lower phosphene threshold. In general this may indicate that the phosphene threshold represents part of a gating mechanism by which more detailed information is propagated as the cortex becomes more excitable (Chaumon et al, 2014). For the PDD group the lack of any divergence from the control group would suggest that the control of sensory gating at the visual cortex is unaffected by Lewy body pathology. However, this conclusion is in contention with findings from post-mortem and electrophysiological investigations which claim that the neural correlates of visual attention/cortical excitability in LBD are impaired by pathology and even related to the presence of VH (Bosboom et al, 2009; Perry et al, 1990; Bohnen & Albin, 2011; McKeith et al, 2004). This hypothesis forms the grounds for the investigation presented and discussed in **Chapter 7**.

In the previous chapter the possibility of disease related compensations in bottom-up attention were discussed in relation to improved VEP P1 latency in those with greater VH severity (**Chapter 5**; Murphy et al, 2015). Possible changes in the local cortical circuitry might extend to the gating of sensory information as performed in the phosphene paradigm (e.g. Romei et al, 2008). Phosphene thresholds have previously shown a positive relationship with the concentrations of excitatory neurotransmitter glutamate (Terhune et al, 2015), yet their density is reduced in patients with PDD (Griffith et al, 2008). The reduction in glutamate might serve as a homeostatic effect to achieve a balance in the state of the visual cortex following the denervation of cholinergic inputs from the nucleus basalis of Meynert (NBM; Liu et al, 2015; Bohnen & Albin, 2011; Gratwicke et al, 2013; Perry et al, 1985; Ruberg et al, 1986; Petrou et al, 2012). Whether these findings are directly related or occur due to changes at different stages in pathogenesis is difficult to determine without a combination of longitudinal cognitive data and the developmental pathology. Nevertheless, it is important to note that the participants in the current study also underwent imaging including spectroscopy of glutamate and GABAergic function in the occipital pole which may help shed further light on processing alterations in PDD.

6.4.3 Mechanisms of Phosphene Perception

The perception of phosphenes was not associated with the modulation of the TEP component amplitudes unlike in earlier studies (Taylor et al, 2010; Baggatini et al, 2015). This was unexpected as phosphene perception has previously been associated with the allocation of a greater number of processing resources (Herring et al, 2015; Taylor et al, 2010; Caparelli et al, 2010), and therefore an increase in the magnitude of the evoked response. However, the lack of an observable difference in the TEP is not to mean that the processing of the information occurs identically. Concurrent imaging and stimulation has been used to identify the networks recruited during phosphene perception vs non-perception (see Caparelli et al, 2010). Phosphene perception has been associated with the recruitment of a more expansive network of sub-cortical regions in addition to dorsal and ventral stream activation. Because EEG is recorded at the scalp surface it is sensitive to the effects of volume conduction and the deteriorating strength of deep sources. It could thus be possible that the lack of a main effect of condition is due to the limitations of EEG rather than there being no differences in how the information is processed.

An alternative proposal is that the identification of phosphenes might have been a more difficult task than intended. Phosphenes will often only appear for a short amount of time and may not possess any distinct features, therefore being difficult for the participant to accurately

recall and be a relatively subtle stimulus. Thus differences between phosphene and non-phosphene trials may be hard to detect from an EEG perspective.

The final possibility that could account for the lack of any differences between conditions is the use of signal decomposition to reduce the interference from the TMS artefacts. Although ICA allows the user to identify an estimate of the elements that contribute to the recorded signals it is possible for some elements to become mixed when there are a high number of dimensions in the data (Korhonen & Illmoniemi, 2010; Hyvärinen, Särelä & Vigário, 1999; Särelä & Vigário, 2003). Although previous work has demonstrated that the use of ICA for TMS artefact reduction is reliable, and does not compromise the overall quality of the TEP (Murphy et al, 2015; Rogasch et al, 2014; Korhonen & Illmoniemi, 2010), there is no guarantee that small amounts of cortical information could not be removed during the process. Conversely, it is possible that the previous studies which show an effect of phosphene perception on amplitude measurements could be reporting data that is exaggerated by the presence of residual artefacts. For example, two of the most recent studies of phosphene TEP's (Bagattini et al, 2015; Taylor et al, 2010) present plots that contain a continuous rising in the TEP potential that does not appear to end within the limits of the epoch. This likely represents the inclusion of very low frequency artefacts caused by the magnetic pulse. The protocol used in the current study aimed to make sure that these were removed and that measurements were done on data with a mean of zero, suggestive of no biases from extra-cortical sources. It is not possible within the scope of this investigation to determine if signal decomposition is the source of the phosphene condition results. However, this identifies an avenue for further research which should aim to characterise the best process for artefact removal/reduction as well as how different manipulations affect the comparison between conditions.

Overall, the lack of differences between the groups would imply that the mechanisms driving phosphene perception are similar in PDD and controls. Additional research using higher spatial resolution is required to confirm this assumption.

6.4.4 Limitations

As mentioned in previous chapters the primary limitation of these analyses is the small sample sizes used. As well as increasing the overall variance in the group distributions this limits the chances of obtaining a comparison across a wider range of VH severity scores. A further limitation of this study is the relative paucity of research providing a background on the properties of the TEP. As a research tool the TEP is still in its infancy, preventing any

deep interpretations regarding its functional and anatomical significance. Future research should aim to study the TEP further in healthy controls, as well as performing a spatially oriented mass-univariate comparison of the PDD and control waveforms (see above). Finally, further work should be performed to better understand the processes underpinning phosphene generation and embrace these to produce a gold-standard method for generating phosphenes using TMS.

6.4.5 Conclusions

The results of this study provide a compelling argument for a range of changes affecting both bottom-up and top-down communication within the visual system in PDD; however, the relationship between these changes and VH generation/severity is unclear. The relatively similar stimulation profiles might reflect homeostatic changes in the systems governing cortical excitability, which may attempt to improve the quality of information input to a system suffering from dysfunctional local and long range communication. However, further work should be performed to understand the physiological generators of the TEP response in PDD patients and how this interacts with the different levels of visuo-spatial attention.

Chapter 7 Posterior Spectral Properties of Parkinson's Disease with Dementia and their Relation to Visual Hallucination Severity

"Quality is never an accident. It is always the result of intelligent effort."

- J. Ruskin (in Lloyd & Mitchinson, 2008)

7.1 Introduction

The visual system is constantly presented with incoming information yet the majority of this will not be relevant to our current locus of attention. To prevent overloading of the visual system irrelevant information is filtered out by the top-down control of neuronal inhibitory properties (Rajagovindan & Ding, 2011). In electrophysiology this can be assessed by measuring changes in the power of the posterior alpha rhythm (8-14Hz). An elegant method of displaying this is the use of visual detection tasks in which participants will display a reduction in alpha power at electrodes over the contralateral hemisphere (Thut, 2006; Worden, 2000). Recently it has been suggested that the alpha rhythm acts to scale the responsiveness of the visual cortex neurons and this can be demonstrated by the observation that the amplitudes of several event related potential components (P1 & P2) appear to be coupled with the phase of the alpha rhythm prior to stimulus presentation (Matthewson et al, 2009; Jensen et al, 2012), thus supporting differences in pre-stimulus cortical microstates as predictors of perceptual outcome (Britz et al, 2014). From a visuo-perceptual perspective this represents a dynamic shifting in the excitability of the occipital neurons in order to improve the chances of detecting salient stimuli, and might be interpreted as a way of gating information processing based on the current context or task demands.

In Parkinson's disease with (PDD) and without dementia (PD) there have been reports of alterations to the global alpha rhythm consisting of a reduction in power and a slowing of the peak frequency in response to eyes closing (Bosboom et al, 2006; Bosboom et al, 2009; Stoffers et al, 2007; Babiloni et al, 2011; Soikkeli et al, 1991). The reduced efficiency of the alpha rhythm in PDD patients implies that the control of goal or context directed attention for perceptual processing is less flexible and likely to impact upon the general visual function and experience in this population. As the cognitive impairment associated with PD and PDD spreads patients begin to demonstrate poorer performance on tasks that require the inhibition of irrelevant visual features (e.g. searching for a target item, Horowitz et al, 2006), or noise that might be misinterpreted (e.g. pareidolic imagery task, Uchiyama et al, 2015). However, there is a paucity of research describing the coupling of performance at such tasks with features of the posterior alpha rhythm in PDD. Given the relevance of the alpha rhythm to the

efficiency of visual perception and detection in healthy controls (Romei et al, 2008; Valera et al, 1981) it's dysfunction in PDD might provide an insight into the contributions of top-down visual control toward the generation of VH. It remains a possibility that the failure to properly gate, in a top-down manner, the processing of incoming visual information might result in an increased load on the visual system which would lead to difficulties in partitioning the signal and matching its elements to their correct proto-objects (e.g. Collerton et al, 2005; Shine et al, 2011).

In this chapter we aimed to, firstly, replicate previous findings of the resting state alpha rhythm in PDD participants relative to controls, and to relate these changes to the severity of visual hallucinations. Secondly we sought to determine whether alterations in pre-transcranial magnetic current stimulation (TMS) alpha power influenced the detection (and non-detection) of phosphenes (e.g. Romei et al, 2008) as a functional assessment of top-down control of early visual cortical excitability in the PDD group.

7.2 Methods

7.2.1 Participants

Resting state electroencephalography (EEG) was recorded from $n = 17$ healthy controls (mean age 75.47 years ± 5.4), and $n = 21$ Parkinson's disease with dementia (PDD) patients. As per previous chapters a total of $n = 10$ PDD participants were not currently taking cholinesterase inhibitors (ChI), whereas $n = 11$ PDD participants were prescribed ChI. All participants participated in a session of combined TMS-EEG but only $n = 9$ controls (mean age 74.78 years ± 4.3) and $n = 9$ PDD participants (mean age 75.11 ± 6.7) reported seeing phosphenes on fifty percent of trials (see **Chapters 3 & 6**). Therefore the analysis of pre-TMS alpha power was limited to $n = 9$ controls and $n = 9$ PDD participants.

7.2.2 Data Acquisition

The experimental protocols for both resting state recordings (eyes open and eyes closed), as well as the combined TMS-EEG recordings are described in **Chapter 6**.

7.2.3 Data Analysis

Data from both resting state recordings, and the TMS-EEG recording, were filtered using a 5-30Hz bandpass filter, bad channels were then removed and the data was decomposed using ICA (TMS-EEG data was first segmented into epochs of the 1024ms prior to the delivery of TMS) to identify and remove motion and ocular artefacts. Additional segments/epochs of the

data containing artefacts were then removed and the bad channels replaced using spherical interpolation (Perrin et al, 1989; Ferree, 2000; Delorme & Makeig, 2004). The power spectral density for all data was estimated using Welch's periodogram (Welch, 1967; Mathworks, 2012) and normalised by dividing each value in the power spectrum by the sum of all values in the power spectrum (e.g. Stoffers et al, 2007; see **Equation 7.1**) to control for possible noise related fluctuations in the power estimate stemming from biological or environmental sources.

$$\bar{g}(f) = \frac{g(f)}{\sum_f g(f)}$$

Equation 7.1, Calculation of relative power (\bar{g}) across the frequency spectrum (f, 5 to 30 Hz). At each point in the frequency spectrum the power ($g(f)$) is divided by the sum of all power values in the frequency spectrum ($\sum_f g(f)$).

The measurement of alpha band activity using the traditional range of 8-14Hz fails to account for functional differences within different sub-ranges of the alpha band. For example, the peak alpha frequency whilst resting with eyes open has been shown to increase during performance of working memory tasks such as the n-back task (Haegens et al, 2014), representing contributions from the activation of different cortical networks (Basar, 2012; Kilmesch, 1999). The peak alpha frequency has also been shown to shift towards a lower frequency in aged controls compared to young controls (Deiber et al, 2013), and participants with dementia with Lewy bodies (DLB) compared to age matched controls (Bonanni et al, 2008). Therefore the caveat in more traditional band based measurements of alpha is the failure to measure the functional specific contributions from sources engaged during a given task. The alpha power for each participant was measured from the individual's alpha peak frequency (IAPF) to improve the functional validity of the measurement (measuring the dominant contributions to engagement of visual attention). The IAPF was identified as the frequency with the highest value in the range of 5 to 14Hz (accounting for the documented slowing of the alpha rhythm in Lewy body dementias, Bonanni et al, 2008) at the occipital region of interest (ROI) during the eyes closed resting state recordings. The IAPF power was then averaged across all electrodes in the ROI for both conditions (**Figure 7.1**).

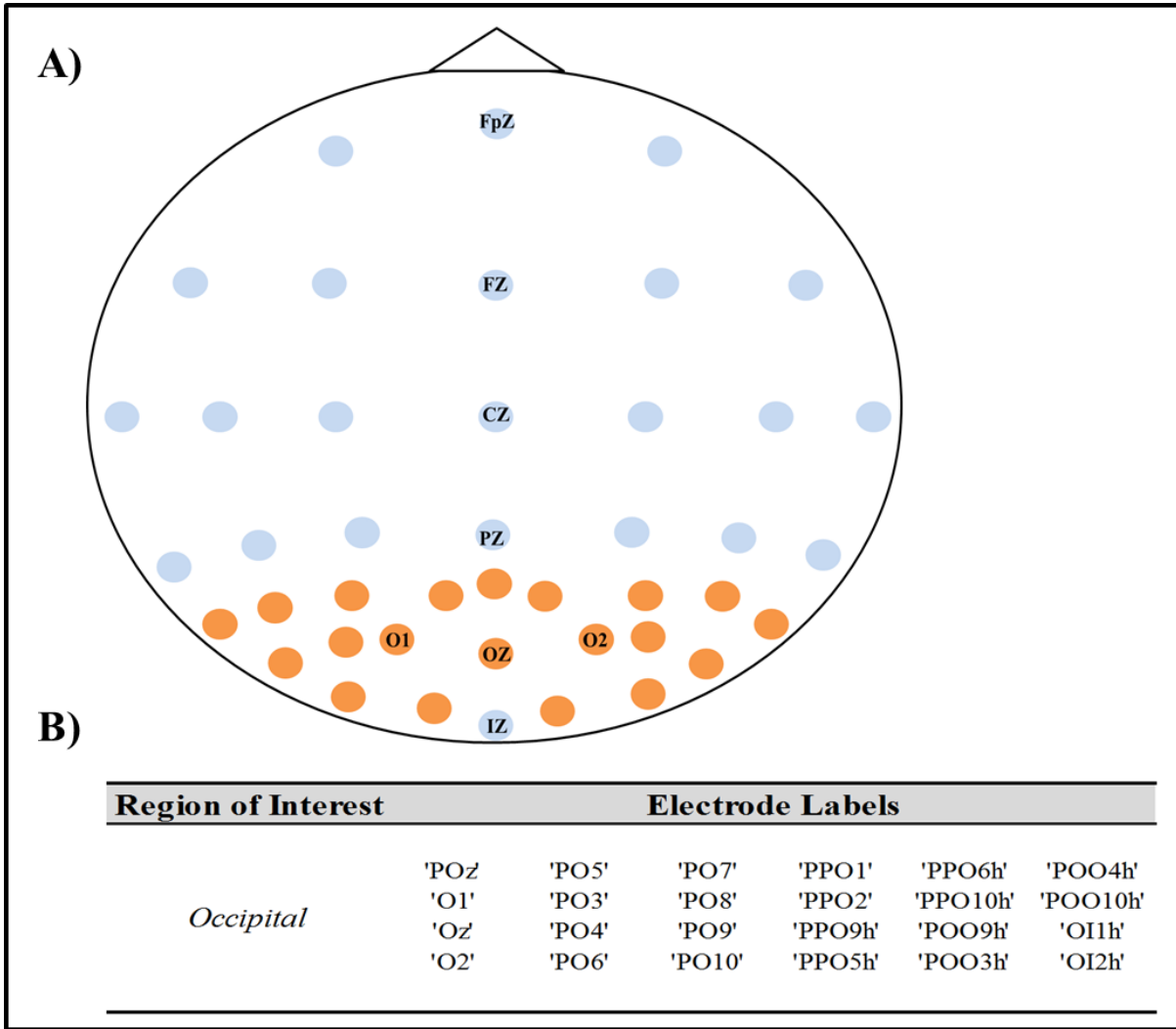


Figure 7.1, A) Schematic depicting the location of the electrodes for the occipital region of interest. B) List of electrodes included in the region of interest analysis.

Reactivity of the posterior alpha rhythm in response to the eyes being opened (α_r) was measured by estimating the difference between ROI averaged IAPF power in the eyes closed condition (α_{ec}) and the ROI averaged IAPF power in the eyes open condition (α_{eo}) as a percentage of the IAPF power in the eyes closed condition (see **Equation 7. 2**).

$$\alpha_r = \left(\frac{(\alpha_{ec} - \alpha_{eo})}{\alpha_{ec}} \right) * 100$$

Equation 7.2, Calculation of relative alpha power reactivity (α_r). Alpha reactivity was measured as the difference between the eyes closed (α_{ec}) and the eyes open condition (α_{eo}) expressed as a percentage of the eyes closed condition.

7.2.4 Statistical Analyses

Covariates

The functional properties of the alpha rhythm have previously been documented as slowing and reducing in power with age (Deiber et al, 2013) and in a number of neurodegenerative diseases changes in the alpha rhythm relative to controls have shown relationships with cognitive fluctuations and global cognitive status (Prichep, 2007; Bonanni et al, 2008; Cromarty et al, 2016; Jeong et al, 2015). Age, mini mental state exam score (MMSE), clinician assessment of fluctuations score (CAF), disease duration, and unified Parkinson's disease rating scale section three total score (UPDRS) were tested as predictors of the variance in EEG alpha power.

Alpha power in PDD has also been shown to be increased as a direct effect of treatment with cholinesterase inhibitors (ChI; Bosboom et al, 2009). It was not possible to ask for participants to refrain from taking prescribed medication, thus to account for the possibility of a dichotomy between those receiving vs not receiving ChI treatment the use of ChI was tested as a predictor using stepwise logistic regression. As in other chapters its effect of variable measurements was compared using the Mann-Whitney U test.

Due to the small sample sizes for the pre-stimulus conditions only correlations were performed. Significant correlations were treated cautiously due to the increased likelihood of spurious findings with limited numbers of samples.

Group Comparisons

Peak Frequency

Peak alpha frequencies were compared between groups using descriptive statistics for each distribution.

Relative Alpha Power

Resting State

Relative alpha power was compared between groups using a 2x2 repeated measures analysis of variance (ANOVA; between group factors = group, PDD vs Controls; within subjects factors = condition, eyes open vs eyes closed). Significant main effects and interactions were followed up using SPSS pairwise comparisons, Bonferroni corrected for multiple comparisons. The relative alpha power reactivity to eyes opening (α_r , see above) was compared between groups using an independent samples t-test.

Pre-Stimulation

The manipulation of the alpha rhythm associated with different perceptual outcomes was studied between groups using the subset of each sample that perceived phosphenes, and contrasted against the alpha rhythm in the two resting state conditions using 2x4 repeated measures ANOVA (between subjects factors = group, PDD vs Controls; within subjects factors = condition, no-phosphene, phosphene, eyes open, eyes closed). Significant main effects and interactions were followed up using SPSS pairwise comparisons, Bonferroni corrected for multiple comparisons. Although the analysis of the pre-stimulus data was limited by its sample size the logic of this approach was that it could be used to conduct a preliminary investigation of the functional vs resting alpha mechanics between the two groups.

Relationship with Visual Hallucinations

In the PDD group relative alpha power values from the resting state and pre-stimulus measurements were tested for a relationship with carer and patient ratings of VH severity using Spearman's correlations. As a preliminary assessment of the perceptual consequences of pre-stimulus neuronal state the relationship between pre-stimulus phosphene, relative alpha power and phosphene complexity (see **Chapter 6**) was tested in both groups using Spearman's correlations.

7.3 Results

7.3.1 Covariates

The results of the covariate analyses are summarised in **Table 7.1**. Resting state alpha power from both conditions, in both groups, was not predicted by any of the demographic variables tested (all $p > .05$). Decline in the pre-stimulus alpha power from the no-phosphene condition was associated with increasing age in the PDD group ($r_s = -.82, p = .01$), as was alpha power in the phosphene condition ($r_s = -.91, p = .002$), but neither were associated with other measures. The control group measurements of pre-stimulus alpha power were unrelated to any of the variables tested. The prescription of ChI was a strong predictor of increased resting state relative alpha power measurements for both conditions in the PDD group (EC, $\beta = .57, p = .043$; EO, $\beta = .51, p = .034$).

Table 7.1 Results of the covariate analyses for both groups.

Group	Variable	Eyes Closed			Eyes Open			Reactivity		No-Phosphene		Phosphene	
		<i>rs</i>	β	<i>p</i>	<i>rs</i>	β	<i>p</i>	<i>rs</i>	<i>p</i>	<i>rs</i>	<i>p</i>	<i>rs</i>	<i>p</i>
Controls	<i>Age</i>	-.18		.5	.08		.76	-.36	.16	-.29	.46	.02	.97
	<i>MMSE</i>	-.13		.62	.24		.36	-.36	.16	-.05	.89	-.08	.84
	<i>UPDRS</i>	-.25		.33	.04		.87	-.35	.17	-.65	.06	-.41	.27
PDD	<i>Age</i>	-.14		.56	-.13		.57	-.04	.85	-.82	.007	-.91	.002
	<i>MMSE</i>	.14		.54	.18		.43	.09	.69	.1	.79	.11	.8
	<i>UPDRS</i>	-.07		.76	-.004		.98	-.32	.16	.31	.42	-.2	.64
	<i>CAF</i>	.12		.61	.06		.78	-.2	.37	-.25	.52	.58	.14
	<i>Disease Duration</i>	.02		.93	.16		.49	-.42	.057	.47	.19	.54	.16
	<i>ChI</i>	.45*	.57	.043	.47*	.51	.034	-.12*	.59				

* Point-biserial correlation

7.3.2 *Peak Frequency*

The IAPF's were significantly lower in the PDD group (mean = 7.1 ± 1.2 , mode = 6) than in the control group (mean = 8.8 ± 1.2 , mode = 8; MWU = 63, $Z = -.37$, $p < .001$), supporting a general slowing of the alpha rhythm (see **Figure 7.2**). The slowing of the alpha rhythm into a "pre-alpha" rhythm (<8Hz; Bonanni et al, 2008) was an exclusive feature of the PDD group, but one which was not influenced by the presence of VH ($\chi^2 = .38$, CV = .13, $p = .65$).

7.3.3 *Resting State Relative Alpha Power*

Analysis of variance revealed a significant main effect of condition ($F(1, 36) = 46.87$, $p < .001$, $\eta^2 = .57$), but not of group ($F(1, 36) = 3.04$, $p = .09$, $\eta^2 = .078$). However, there was a significant interaction between the participant group and the condition on the relative alpha power ($F(1, 36) = 12.92$, $p = .001$, $\eta^2 = .26$). Follow up pairwise comparisons revealed that relative alpha power was generally greatest during the eyes closed condition ($p < .001$, CI, lower .09, upper .17). Examination of the interaction was carried out by comparing the alpha reactivity (difference between conditions as a percentage of the eyes closed alpha power, see above) between groups using an independent samples t-test. This revealed that the reactivity of the alpha rhythm as a result of the eyes being opened was significantly greater in the control group (41.74% reduction $\pm 19.8\%$) than in the PDD group (13.3% reduction $\pm 19.5\%$) ($t(36) = 4.44$, $p < .001$, $d = 1.5$, CI, lower 15.5% upper 41.5%). In the PDD group the resting state alpha power measurements were not related to carer or patient measures of VH severity (see **Table 7.2**). Resting state alpha patterns are visualised in **Figure 7.3**.

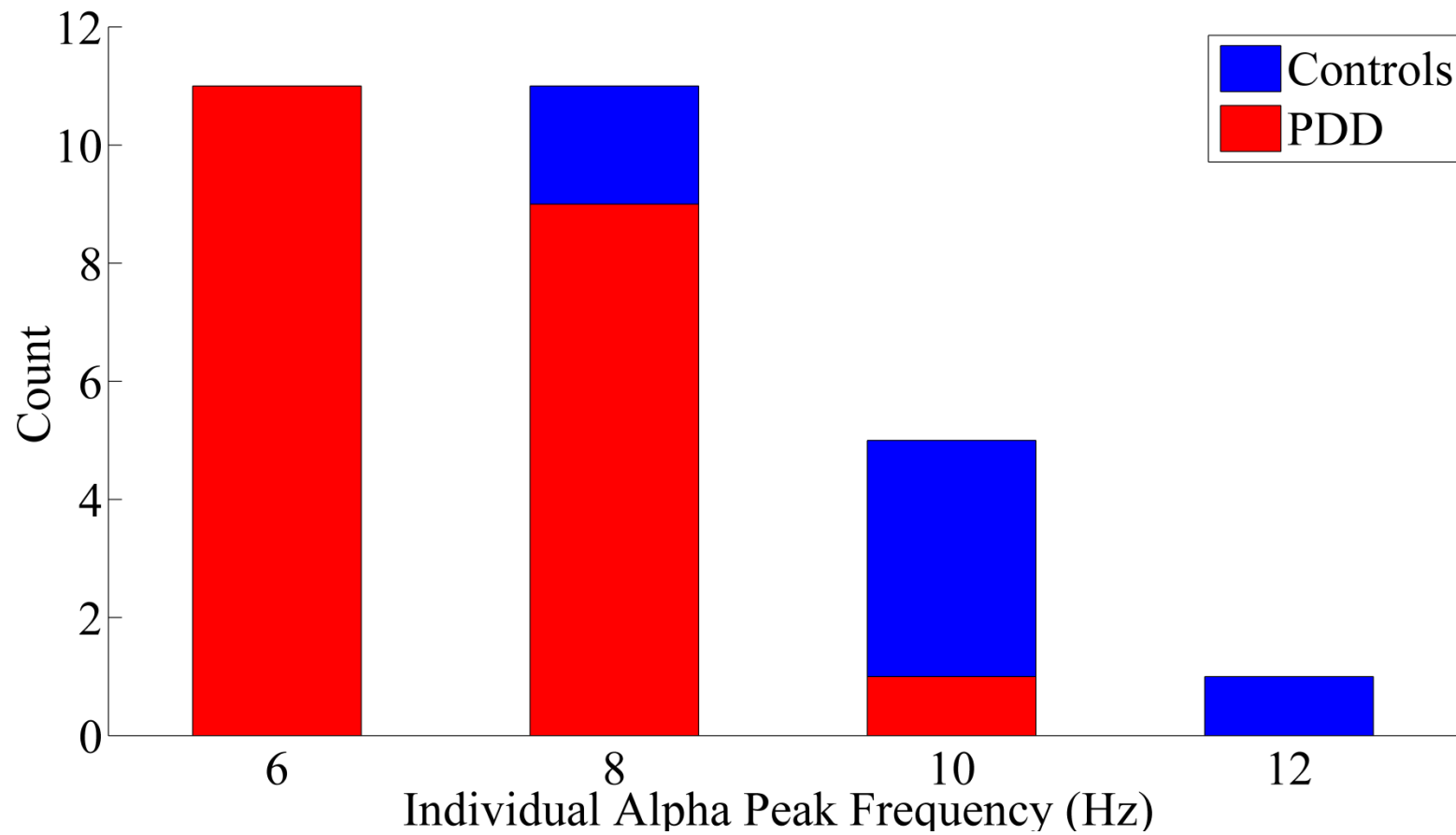


Figure 7.2, Stacked distribution of individual alpha peak frequencies for the control group (blue) and the PDD group (red). The PDD group demonstrated a tendency to shift towards a slower alpha peak consistent with previous findings (e.g. Bonanni et al, 2008).

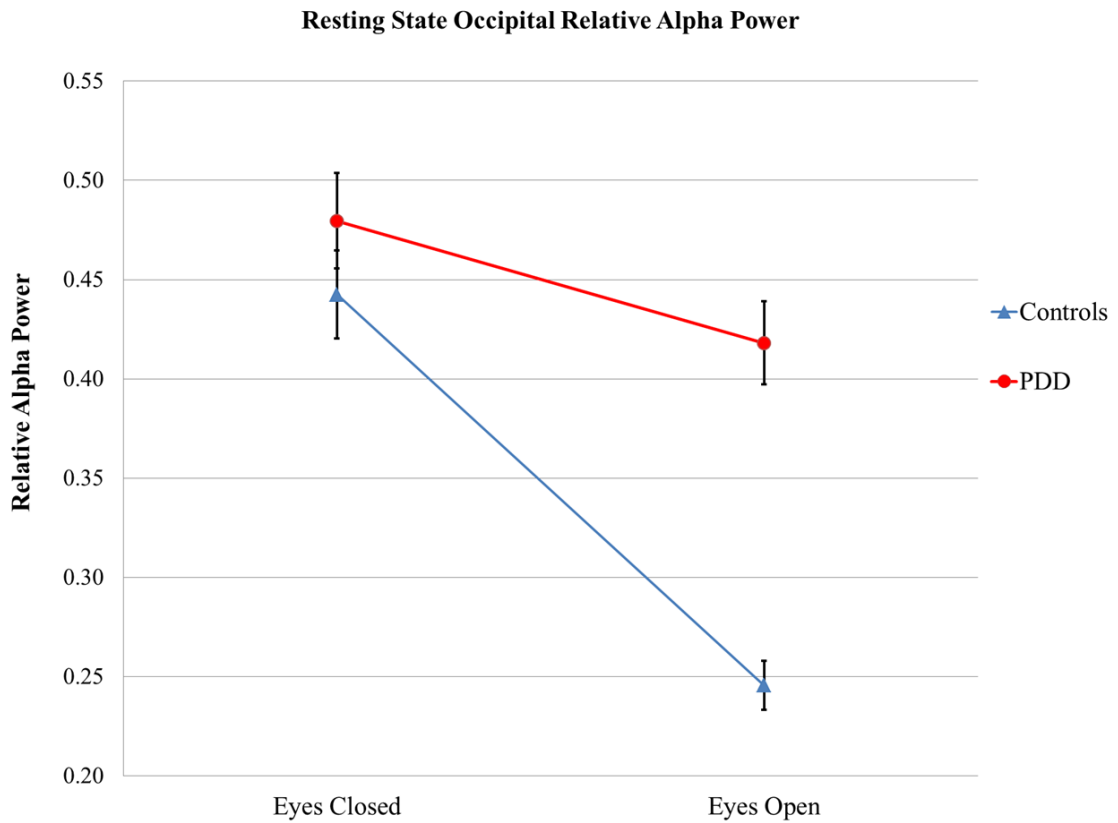


Figure 7.3, Resting state occipital relative alpha power compared between conditions for both groups. Both groups demonstrate the characteristic reduction in alpha power in response to eyes opening, however this is noticeably impaired in the PDD group.

Table 7.2, comparison of carer and patient ratings of VH severity correlated with resting state alpha power values.

Variable	NPI Hallucinations		NEVHI	
	<i>rs</i>	<i>p</i>	<i>rs</i>	<i>p</i>
<i>Eyes Closed</i>	-.05	.82	-.005	.98
<i>Eyes Open</i>	.01	.96	.02	.93
<i>Reactivity</i>	-.19	.38	-.11	.63

7.3.4 Effects of Cholinesterase Inhibitors on Resting State Relative Alpha Power

Relative alpha power was increased in both conditions in PDD patients taking ChI (Eyes closed, $MWU = 27, Z = -.19, p = .049$; Eyes open, $MWU = 27, Z = 1.9, p = .049$). However, there was no improvement in the reactivity to eyes opening in those patients taking ChI compared to those not taking them ($MWU = 41, Z = -.98, p = .35$). See **Figure 7.4**.

7.3.5 Effects of Pre-Stimulus Relative Alpha Power on Phosphene Perception

Analysis of variance revealed a significant main effect of condition ($F(2.33, 34.96) = 19.83, p < .001, \eta^2 = .57$) but not of participant group ($F(1, 15) = .31, p = .58, \eta^2 = .02$). There was no significant interaction ($F(2.33, 34.96) = 2.11, p = .13, \eta^2 = .12$). Pairwise comparisons identified a failure of the phosphene condition alpha power to significantly diverge from the no-phosphene condition alpha power ($p = 1, CI \text{ lower } -.005, \text{ upper } .013$). However, alpha power in both of the pre-stimulus conditions (during which the participant's eyes were closed) was significantly reduced compared to the alpha power in the resting state eyes closed condition (*phosphene*, $p < .001, CI \text{ lower } -.29, \text{ upper } -.09$; *no-phosphene*, $p < .001, CI \text{ lower } -.28, \text{ upper } -.08$). See **Figure 7.5**.

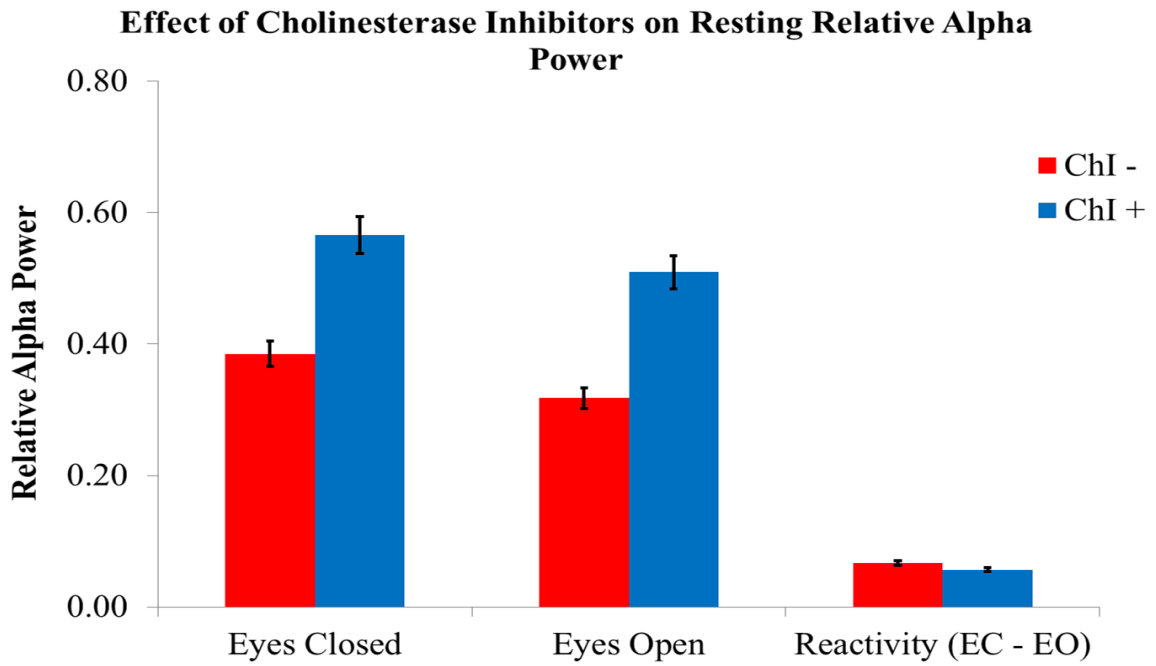


Figure 7.4, Comparison of the effects of cholinesterase inhibitor (ChI) use on patterns of resting state alpha activity in Parkinson's disease with dementia (PDD) patients.

Comparison of Resting and Pre-Stimulus Relative Alpha Power

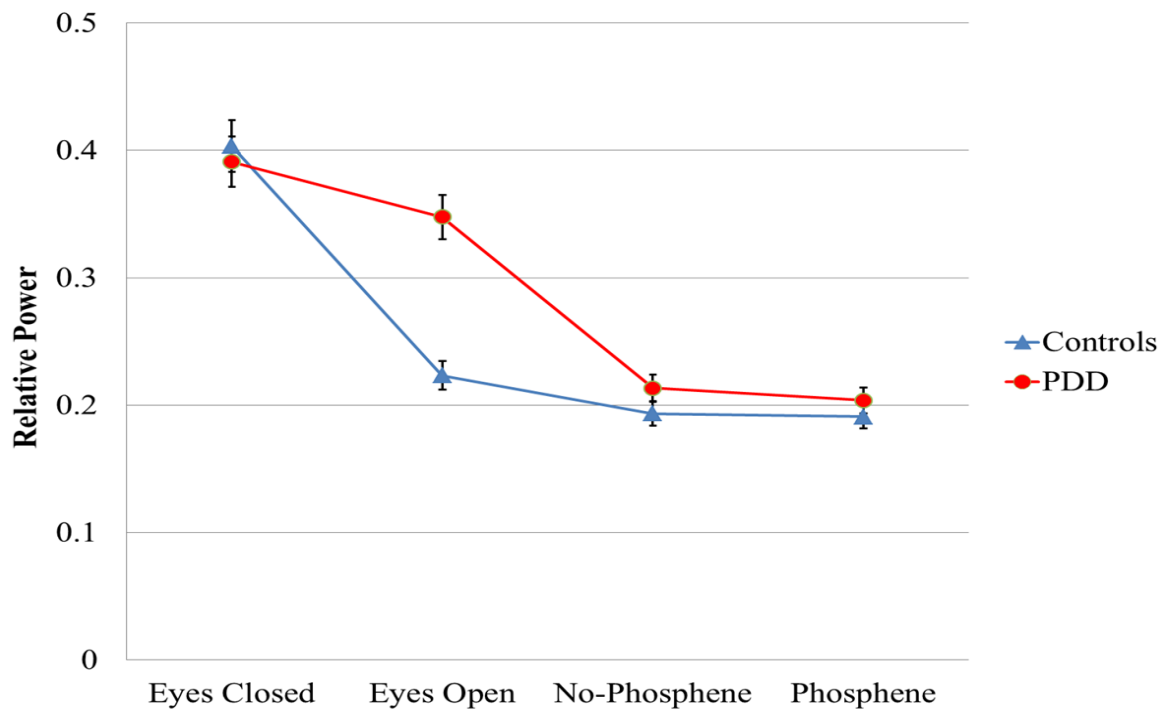


Figure 7.5, Comparison of resting state and pre-stimulus relative alpha power between groups. Both groups show a decrease in alpha power when opening eyes, yet pre-stimulus alpha power (with eyes closed) is further reduced in power compared to the resting eyes closed condition.

7.4 Discussion

In previous work the alpha rhythm has been used as a marker for the control of attention (Händel et al, 2011; Ergenoglu et al, 2004; Foxe & Snyder, 2011), and hypothesised to primarily represent cholinergic control over the excitation of neuronal populations (Rjagovindan & Ding, 2011; Chaumon et al, 2014; Bosboom et al, 2009; Vanderwolf & Stewart, 1988). The disruption of the resting alpha rhythm in neurodegenerative diseases and dementia has been linked to fluctuations in cognition (Jeong et al, 2016; Prichep, 2007; Cromarty et al, 2016), working memory (Hogan et al, 2003), and global cognitive status (Babiloni et al, 2011; Babiloni et al, 2008). In PD and PDD the general reduction in alpha power is thought to reflect the deafferentation of neo-cortical cholinergic inputs following the denervation of the nucleus basalis of Meynert (NBM; Perry et al, 1985; Liu et al, 2015; Gratwicke et al, 2013), whereas the slowing of the peak alpha frequency is believed to be primarily the result of lesions to several neurotransmitter systems (e.g. Noradrenergic, Berridge et al, 1993; serotonergic, Vanderwolf & Baker, 1986; dopaminergic, Kropf & Kuschinsky, 1991) projecting from the brainstem (Babiloni et al, 2011; Berridge et al, 1993; Vanderwolf et al, 1990; Bosboom et al, 2006).

The results of the current study replicate previous findings demonstrating that the peak frequency of the alpha rhythm was slower in the PDD group, regardless of medication or psychiatric symptoms (VH), reflecting a greater likelihood of a peak in the high theta (6Hz) or “pre-alpha” range (e.g. Bonanni et al, 2008; Stoffers et al, 2007; Caviness et al, 2007; Kotini et al, 2005; Bosboom et al, 2006; Neufeld et al, 1994). Conversely, peak relative alpha power was not significantly different between the groups, although there was a significant increase in power associated with the prescription of ChI. This suggests that potentially these medications may help to normalise the magnitude of the alpha rhythm, although clearly a caveat is that the effect of these medications is being examined in cross-sectional rather than pre and post administration preventing causal links with changes in relative alpha power from being determined.

Furthermore, despite the benefits offered by ChI intervention in some of the PDD participants, the overall reactivity of the PDD participants to eyes opening was reduced in comparison to the control group, with relative alpha power not significantly different between conditions. This has previously been reported in PDD (Bosboom et al, 2006) and in Alzheimer’s disease (Berendse et al, 2000; Wada et al, 1997), and posited to be driven by a diminished cortical response to photic stimulation (Wada et al, 1997).

The study of the posterior alpha rhythm is important for understanding the roll of the top-down control of the early visual system in the generation of VH. However, the current data did not indicate a relationship with the severity of VH in the PDD group, suggesting that the factors which selectively scale the responsiveness of neurons in the visual cortex are not a causative factor for VH. Whilst this does not rule out the contributions of top-down dysfunction towards the generation of VH in PDD it does imply that VH are more likely to arise due to failures in efficiently managing attention at a higher perceptual level than perhaps the early visual cortex. A possible interpretation of this is that reduced control of the inhibitory properties of the visual cortex neurons results in a slightly more erratic visual input, yet this is only a problem when higher perceptual networks such as those described in the integrative approach (Collerton et al, 2005; Shine et al, 2011) begin to show signs of functional disconnection from top-down systems (Peraza et al, 2014). Thus a combination of bottom-up deficits and top-down deficits is required for the manifestation of VH. However, without a longitudinal account of posterior alpha changes, or neuropathology to accompany each participant it is impossible to draw conclusions of the physiological contributors within this dataset. Additionally, given that the range of VH only reaches a moderate stage of severity, it could be that the reduction in the control of cortical excitability contributes more in those patients with advanced and severe VH.

Regarding the phosphene task, it was surprising to discover that neither group demonstrated a significant reduction in relative alpha power prior to trials in which a phosphene was present, something which has been reported in previous studies (e.g. Romei et al, 2008). The lack of dissociation between the groups raises the possibility that this could stem from the methods utilised in the data processing, or within the paradigm design itself. For example, Romei et al, (2008) transformed the data to represent event related de/synchronisation in the alpha band which allowed them to assess fluctuations in the power of the alpha band over time. This revealed that alpha power begins to decrease several hundred milliseconds prior to stimulation, yet this fluctuation might not be strong or long enough to influence the measurement of alpha power over ~1000ms using an averaging measure such as power spectral density as was applied in the analyses presented here.

During stimulation participants were instructed to keep their eyes closed (e.g. Taylor et al, 2011) so that phosphenes might be noticed more easily rather than having to compete with external distractions, and to limit false negatives particularly in cognitively compromised individuals. This was balanced by including regular breaks to prevent cortical adaptation to the lack of light

(Boroojerdi et al, 2000) and thus measuring the natural state. However, the result of closing the eyes is typically a maximal increase in resting state alpha power. Therefore this might be expected to result in a masking of large scale functional differences by a ceiling effect on the resting alpha power. Contrary to this the preliminary comparison of resting versus pre-stimulus alpha power demonstrated that whilst there is no difference in power between the pre-stimulus conditions, maximal resting state alpha power during eyes closed resting is significantly increased relative to the alpha power preceding stimulation. It is possible that this reflects an anticipatory activation of the visual system whereby the visual cortex neurons are modulated in response to the task demands (i.e. being asked to report the appearance of phosphenes). Horowitz et al, (2006) have previously demonstrated that PD participants can make use of external top-down information (e.g. a constantly present task description) to improve performance on visual search tasks (Horowitz et al, 2006), showing problems with internal management of top-down control. Therefore the ability to modulate alpha power in response to task demands similarly to controls could point towards a compensatory mechanism aiming to improve visual performance. For example, the resting alpha power and the reactivity to eyes opening in PDD represents very conservative control of neuronal gain. However, this is drastically reduced to meet task demands, with the outcome being a state of much less constrained neuronal gain control. The consequence of this could be that the system is now overactive to improve the chances of detecting stimuli (e.g. Pajani et al, 2015), but as a result of this improved function becomes more exposed to the possibility of VH. More work should be conducted, with a larger and more varied clinical sample, to better understand this mechanic and its role within the framework of VH generation in PDD. Further, to bring clarity to the methodological issues arising from this study a future comparison should be made between this paradigm and that used by Romei et al, with the aim of deriving a gold-standard for pre-stimulus measurements of excitability.

7.4.1 Limitations

The main limitations of this study are related to the samples recruited as discussed previously in other chapters. Larger samples would help to reduce the variance in each group and would strengthen the hypothesis testing. Furthermore the PDD group was limited to considering VH within a relatively narrow range of severity scores. It has already been suggested that it is perhaps more robust to consider VH in this manner as opposed to a dichotomy (i.e. hallucinations present vs absent), yet without information from those who experience more severe VH the

analysis falls short of describing a true relationship between the experience of hallucinations and the physiology of this participant group.

7.4.2 Conclusions

The results of this study reflect previous findings of disrupted posterior alpha rhythms in participants with PDD. Although these changes are not related to the severity of VH they might represent a pre-requisite transition towards a less vigilant application of top-down control in PDD patients. The resting state alpha power was increased in PDD participants receiving cholinergic treatment suggesting that these changes could possibly stem from deafferentation of cholinergic projections to the neo-cortex. Although speculative this could represent that the slowing of the alpha rhythm reflects disrupted cortico-cortical control between the visual and executive cortices. Future work should expand the sample sizes and include PDD participants with a wider range of VH severity scores. Although there is no direct relationship between alpha rhythm properties and the experience of VH the disruption of a filtering mechanism such as this could influence the phenomenology of the hallucinations. All future investigations should consider the use of a longitudinal study design to more clearly identify possible developmental markers of VH experience.

Chapter 8 Conclusions

*“The deepest solace lies in understanding, this ancient unseen stream, a shudder before the beautiful” –
Chandrasekhar, S. (1910-1995)*

Visual hallucinations (VH), particularly those which are complex and often recurrent, as noted in the introduction are a common symptom of dementia in Parkinson’s disease (PDD; up to 65% of cases, Aarsland et al, 1999; McKeith et al, 2005; Emre et al, 2007). As well as being associated with a steeper pattern of cognitive decline (Park et al, 2013; Santangelo et al, 2007), they can also lead to greater distress and care giver burden (Ricci et al, 2009; Factor et al, 2003), eventual nursing home placement and mortality (Goetz & Stebbins, 1993; Goetz & Stebbins, 1995). Despite the serious implications that this holds for patient quality of life the history of previous research has failed to provide a complete understanding of their aetiology, making the treatment of this symptom a difficult task. The school of thought surrounding how VH are generated in PDD has gradually developed to consider that illusory percepts do not simply arise from the malfunction of a single region for perceptual processing, as believed for many decades (ffytche, 2007). Instead the consensus is now that VH are the product of dysfunctional communication across multiple networks, coupled with degraded visual input (e.g. Collerton et al, 2005; Shine et al, 2011; Diederich et al, 2004; Tsuakada et al, 2015). Despite this theory being supported by a wealth of structural and functional neuroimaging results there remains a paucity of research concerning the mechanistic side of VH generation.

The VEEGStim study (see **Chapter 3**) was designed to better understand the neurophysiology associated with VH in PDD, and in what manner this is different to the perceptual physiology in healthy controls. The investigations described in this thesis were intended to shed light upon how the electrophysiological signatures of synaptic communication attributed to top-down and bottom-up visual processing were affected by PDD pathology, and how this was related to the development of VH.

8.1 Summary of Main Findings

The results of these investigations provide evidence of bottom-up and top-down impairments in PDD relative to controls, as well as an insight into their relationship with the experience of VH. In the visual evoked potential study (**Chapter 5**) although the PDD component amplitudes were

reduced (demonstrating poor retinal quality) there was a sign of intact transmission between the retina and the primary visual cortex, demarcated by the N1 component latency. Despite the early similarities between groups this was followed by a pattern of decreasing P1 latency as the experience of VH was rated as being more severe. In the TMS evoked potential (TEP) investigation (**Chapter 6**) there were striking similarities in the amplitude and latency measurements for all components, irrespective of regions, between groups. However, this was offset by differences in the activity occurring between components at multiple periods in time post-stimulation. There was no strong relationship between the output of TEP and the severity of VH experience. Finally, the investigation of the posterior alpha rhythm (**Chapter 7**) replicated previous findings of a slowed peak alpha frequency, and reduced reactivity to eyes opening. Despite conforming to previous results, and their implied involvement in visual perception (see **Chapters 1 & 7**), the measurements of the posterior alpha rhythm did not demonstrate any relationship with the severity of the VH experience.

For more detailed interpretations and evaluation of the individual findings please refer to the discussion sections in **Chapter 4** (demographics & baseline testing), **Chapter 5** (visual evoked potential), **Chapter 6** (TMS evoked potential), and **Chapter 7** (posterior alpha rhythm).

8.2 Conclusions

8.2.1 Demographics & Baseline Profiles

Investigation of the demographic factors, cognitive profiles, and visual complaints experienced by both groups of participants, revealed that the study sample being used was consistent with those used in previous studies with PDD patients showing a pattern of cognitive decline including memory loss, executive impairment and visuo-spatial difficulties, relative to the control sample. However, due to (approximately) half of the patients receiving cholinesterase inhibitors it was necessary to investigate sub-group differences in the measurements of the stimulation profile, transcranial magnetic current stimulation (TMS) evoked potentials (TEP), and posterior alpha power given the prior data suggesting that the function (and dysfunction) of the cholinergic system may have a significant role in the occurrence of VH. We found however that medication was unrelated to the results of the TMS study although notably use of cholinergic medication in PDD patients was associated with improvements in alpha power, which is consistent with previous findings in the literature (Bosboom et al, 2009).

8.2.2 *Electrophysiology*

The combination of the findings from this series of studies provide clear evidence of dysfunctional bottom-up and top-down communication related to visual processing in patients with PDD. However, the relationship between visual processing and the experience of VH (in terms of the NPI hallucinations subscale severity*frequency [VH severity], and adapted NEVHI scores, **see Chapters 3 & 4**) was not a case of a simple linear decline in visual processing efficiency (as inferred from electrophysiological measures), as the VH experience became more pronounced. Instead, within the range of VH severities in the PDD group examined in this thesis, it appears that there is disturbed communication between executive and perceptual regions coupled with poor quality visual input. In particular, in the VEP analysis (**Chapter 5**) we found that as the VH experience becomes more pronounced as the time taken for visual input from the retina to arrive at cortical perceptual processing centres decreases. This opens up the possibility that there might be a trend towards compensatory changes in bottom-up attention at the primary visual cortex. However, more in depth analyses will be required to determine the true nature of this trend. Overall, these findings suggest that the impairments observed in top-down (**see Chapter 7**) and bottom-up processing (**see Chapters 5 & 6**) are pre-requisite factors for the experience of VH. This interpretation fits well within the narrative set by the integrative approach to understanding VH (Collerton et al, 2005; Shine et al, 2011; Diederich et al, 2004), and should provide a solid foundation for more detailed analyses of synaptic and network dynamics related to the experience of VH.

8.3 Critique and Future directions

8.3.1 *Study Design and Analysis*

The studies presented help to demonstrate the importance of contributions from bottom-up and top-down processing systems for the experience of VH in PDD. However, the conclusions made (as well as the scope for conclusions concerning the relative balance of the bottom-up and top-down processes in the formation of VH) are limited by a number of factors, most notably the group sample sizes. Whilst the ideal a priori sample sizes required are unknown, the current sample sizes may be insufficient to estimate accurate effect sizes – particularly in the PDD population. The relationship between electrophysiological measurements and VH was compared using a scaled correlative approach (**see Chapters 2 & 3**), however, correlations are particularly sensitive to leverage effects exerted by data points that are even slightly outlying, particularly if

sample sizes are relatively small. Furthermore due to the small sample sizes the problem of leverage effects makes it unfeasible to perform more detailed modelling such as structural equation modelling (SEM), or multiple regression to explore the impact of several variables at once.

In addition to the effects of the sample size on the statistical tests it is also worth highlighting that a smaller sample size is less likely to approach a true representation of the population. Whilst the demographic factors show that the cognitive and clinical profiles of the PDD group were appropriate, there is an under-representation of the experience of VH as a whole within the PDD sample as there are few participants with very frequent/severe hallucinations. This brings into question whether or not the relationships seen between VH severity and the electrophysiological measurements would hold with a greater range of NPI hallucinations subscale VH severity scores, or whether a different pattern might emerge.

8.3.2 Transcranial Magnetic Current Stimulation Evoked Potentials

The findings from the TEP study raised questions about the most suitable methodology for analysing concurrent TMS and electroencephalography (EEG) waveforms. Observation of group TEP waveforms at the occipital and parietal cortices revealed multiple distinct differences in the amplitude-latency pairings resembling a slowing of the PDD waveforms during the transition between components (regardless of VH status). In this case there was a quantifiable and significant difference between the group waveforms implying that whilst the component peaks were generated similarly to the controls (given there were no significant differences in the peak amplitudes of the components) the processes of electrical activity “between” peaks appeared to be altered in the PD group. To this extent the use of mass-univariate waveform analysis is a strength which makes it possible to analyse periods of activity that occur outside of the traditional component windows which can be used to add depth to the interpretation of results. Future application of this approach to similar data could benefit from making use of more advanced methods for the control of familywise error rate, such as cluster or pixel based corrections, allowing for the inclusion of all electrodes simultaneously and thus also improving the spatial resolution of the data. Additionally, given the observation of a possible slowing of activity it would be beneficial to mimic this approach whilst using time-frequency transformations of the data such as wavelet analysis; previous investigations of the TEP’s spectral properties in healthy controls have shown large contributions from alpha and theta oscillations (Garcia et al, 2011;

Herring et al, 2015), which are known to be affected in PDD (Bosboom et al, 2006; Stoffers et al, 2007; Bonanni et al, 2008). Therefore the use of mass-univariate wavelet analyses might help to shed light on which populations of neurons contribute to the TEP response (and by extension basic visual perception) and how they are affected by PDD pathology. Confirmation that this apparent slowing is a common factor across cases of PDD might also help in the development of a physiological marker for use in future experiments, although clinical use would be limited by issues of technical difficulties in acquiring TMS EEG data and skills required for processing of the data which are time-consuming.

Removal of TMS Artefacts

The removal of TMS artefacts from the EEG data in this study was performed using an approach centred on independent components analysis (ICA), which although it has been demonstrated as reliable and without damage to the integrity of the evoked response (e.g. Korhonen et al, 2011; Murphy et al, 2015; Rogasch et al, 2014), is still far from perfect and does not currently adhere to a generalised set of criteria for use. In the current study it was addressed that whilst ICA could be used to remove the larger TMS artefacts the decomposition was often susceptible to over-fitting and thus failing to fully separate some of the slow-wave magnetic contributions from the cortical contributions to the mixed signals. To account for this empirical mode decomposition (EMD; Huang, 1998) was applied, which allowed for the removal of slow wave (delta band, 1-3Hz) distortions, thus improving the validity of the TEP measurements. Further work is required to determine the most efficient method of using signal decomposition algorithms to identify and remove TMS artefacts from EEG data, and further to develop a gold-standard approach. The latter would improve the ability to replicate findings between laboratories, therefore improving the validity of studies reporting on the TEP.

Phosphenes for Studying Visual Perception

Finally, when considering the use of phosphenes to study active versus passive visual perception it is important to understand that there does not exist a consensus on a best or most efficient method for their elicitation. Likewise there is scant research available which has sought to model or study the properties of stimulation and their interaction with different populations of neurons leading to the development of phosphenes. In this study phosphenes were reported in roughly half of each participant group, despite the use of the same procedure and clinical similarities between individuals. Slight improvements in response rate were previously noted when using a

paired pulse TMS paradigm (Taylor et al, 2011), but it remains unclear as to what implications the application of a priming pulse prior to the main pulse might have for the interpretation of the general physiology between groups. Whilst phosphenes can to a degree be objectively tested for and measured it is clear that the methods for their study are not completely developed. In the current study phosphenes were elicited and reported on whilst the participant had their eyes closed, whereas in several earlier studies (e.g. Kammer et al, 2005; Taylor et al, 2010) the paradigms used required the participants to have their eyes open but fixating their gaze on a blank screen or canvas. Whilst both have applied different methods to ensure that attention (and gaze) is fixated, thus minimising distractors, these paradigms both invoke separate physiological states which diverge in terms of cortical excitability (Boroojerdi et al, 2000; Barry et al, 2007), yet are both capable of eliciting a response. Although their continued use in experiments on conscious perception will remain valid, the lack of knowledge concerning the mechanisms and pathways that lead to phosphene generation is a severely limiting factor for both paradigm design and data interpretation. A primary step towards understanding how to efficiently utilise a phosphene paradigm would ideally begin with a meta-analysis of methodologies and their resulting phosphene response characteristics to identify commonalities and a point from which to move forwards in understanding. In a previous investigation Caparelli and colleagues (Caparelli et al, 2010), using a combination of TMS and fMRI, demonstrated a divergence in the anatomical pathways activated during phosphene and no-phosphene perception (see **Chapter 6**). This work should be expanded to aid the understanding of their physical mechanisms and how these might be altered by differences in methodology.

Appendices

- 1. Information & Consent Forms**
 - 1.1. Example of Information sheets for controls**
 - 1.2. Consent form for controls**
 - 1.3. Consent form for patients**
 - 1.4. Consent form for carers**
- 2. Phosphene Complexity Questionnaire**
- 3. Poster Presented at the British Neuroscience Association Meeting April 2015: Reliability of ICA for the Removal of TMS artefacts in EEG**
- 4. Individual Participant Global Field Power Peak Latencies used for the TMS Evoked Potential Component Windowing**
- 5. List of Publications**

Appendix 1.1 – Example of Participant Information Sheet

The Newcastle upon Tyne Hospitals 
NHS Foundation Trust



Participant Information Sheet

Biomedical Research Unit: Visual hallucinations:

an EEG and non-invasive Stimulation study

(BRU VEEG-Stim Study)

You are being invited to take part in a research study. This leaflet explains why the research is being done and what taking part will involve. Please read the following information carefully and discuss it with others if you wish. You can then talk to the researchers before you decide whether to go ahead. Thank you for reading this.

What is the study about?

People with Lewy body dementia or Parkinson's disease often experience visual hallucinations and problems with how they perceive things. These symptoms can be very distressing for the people that experience them.

Currently we don't fully understand why and how these hallucinations occur although we think that changes in the parts of the brain which deal with vision are important. Knowing more about how and why hallucinations occur will help us develop better treatments.

To help us understand more, we want to carry out a study to look at which parts of the brain are involved in producing the visual hallucinations and will be testing people with hallucinations. However to understand better which parts of the brain go wrong in people who hallucinate it is very important that we compare our findings against people who don't experience hallucinations or have dementia and for this reason we have approached you to take part.

The study involves 2 different tests and up to 4 visits.

The first of these is Magnetic Resonance Imaging (MRI). This is an established method of making pictures of the brain. We plan on using this technique to look at the structure of the brain, and how active different parts of the brain are. We want to test people who experience visual hallucinations and compare them to people who do not experience hallucinations.

The second test we would like to carry out would be one called transcranial magnetic stimulation (TMS) combined with electroencephalography (EEG). TMS allows us to rest a hand-held device on a subject's head which very briefly stimulates different parts of the brain whereas EEG involves putting a special wired cap on the head which records the brain's response to the TMS. This will then be able to tell us which parts of the brain might be involved in the production of visual hallucinations and we will compare findings in patients against healthy people or controls.

What does taking part involve?

The study consists of 4 steps:

Baseline Assessment (Visit 1: 2 hours)

On the first occasion you will be asked some questions about your general health and mood, and have some short memory tests and vision tests as well as some short attention tests on a computer. This part of the research will take place in your own home, although if it is easier you can come to the Clinical Ageing and Research Unit (CARU) in Newcastle.

MRI scan (Visit 2: 1 hour)

On another day you would have a MRI scan at the University MR scanner facility. Before going into the scanner we will ask you some brief questions about your attention and concentration. In the scanner you will lie still on a couch in the MRI scanner (see picture) and during the scan we may ask you, depending upon your vision, to look a flashing checkerboard on a screen and press a button when you see a red dot. Otherwise you will be asked to relax and lie with your eyes closed.

TMS/EEG test (Visit 3: 2 hours)

On the next visit we will ask you to come to CARU to have the TMS/EEG test. Again, just like the MRI scan visit we may first ask you some brief questions about your attention and

concentration. After this we will sit you in a chair upright and put on the EEG cap (see picture). This is a special cap with electrical sensors which sits on your head and picks up the tiny brain wave signals. This sensor mesh is very easy to put on and doesn't cause any discomfort although we will put a clear gel through little holes in the cap to make sure that the sensors make good contact with your head.

For the first part of the test, depending upon your vision, we may ask you to look at a flashing checkerboard image while recording your brain activity. After this, we will carry out the TMS study.

For this part of the visit, we will put the TMS device against the back of your head and the room will be darkened. You may be asked to wear an eye mask as well. The technician will move the device around your head and try and activate the visual part of your brain. You might experience movements in your hand muscles or you might see flashes of light. You would be asked when you experience these flashes of light and the technician would make a note of this. The stimulation is not painful and feels like someone tapping your head. Once we have worked out where we can get reliable brain activity we will give a series of pulses.

We may also in a subgroup of participants, carry out a quick recording of motor function. We will attach two recording pads after gentle cleaning to your hands and we will make some recordings of the muscle movements. These tests will help us with our reliability measures.

Throughout the testing you would be given regular breaks and the technician would be present throughout. If you found that you did not want to continue, you would be able to ask the technician to stop the test at any time.

The technician performing the TMS will communicate with you throughout the test to check that you stay comfortable and you would be given regular breaks. If you are uncomfortable, you can end the test at any point. Ask the technician to stop the test at any point.

TMS/EEG retest (Visit 4: 2 hours)

On the final visit we will ask you to come back and have the TMS/EEG test repeated again that you had done on visit 3. This aspect of the study will allow us to check the reliability and validity of our recordings. We only need to ask a sub-group of people to have this retesting done **so if you do not want to have this done, then this would be absolutely fine.**

Are there any risks?

MR scan - There is no radiation known to be associated with the scan. There are no known serious risks, and the scan is not painful. The only discomfort some people feel is of claustrophobia or feeling uncomfortable from lying still while in the scanner. You would be able to leave the scanner at any time you wish. The radiographer performing the scan would communicate with you throughout the scan to check that you stay comfortable. You would be provided with a hand held buzzer, which you could use to end the scan at any point. Also, should you wish, someone can be with you in the scan room at all times. If you are uncomfortable, you could end the scan at any point.

EEG cap - The cap may cause some reddening of the skin on the head where the sensors are attached but this disappears within half an hour after the sensor mesh is removed. Also sometimes the gel we use can cause the hair to be a bit sticky after the test but this washes out very easily with warm water.

TMS test - TMS is not painful and feels like someone tapping your head – so it can be more irritating than uncomfortable. About one in ten people experience a headache or neck stiffness afterwards, which can be easily treated with paracetamol. TMS has been used safely in tens of thousands of subjects worldwide without any long-term side effects and we have significant

experience of using this test in people who hallucinate here in Newcastle. Extremely rarely, however (never in our facilities), people can experience a seizure with the stimulation, particularly if they have had seizures in the past. This event is very unlikely to happen to you in the present study. However, just in case, we have access to emergency equipment to treat you, if needed.

How does this study benefit me?

This study doesn't have any direct benefits for you as it is an observational study which is trying to understand how the brain causes hallucinations. However the findings from the study may, in the future, help someone who has visual hallucinations.

Study outcomes

At the end of the study the key findings will be sent to participants in the form of a newsletter to highlight how their participation has aided with the study research. The study researchers will also organise an open day where participants will have the opportunity to find out more about the study findings, how the findings will be communicated and an opportunity to ask questions.

This study is being undertaken as part fulfilment of an educational project (PhD) and it is planned to publish the findings in peer review articles and to present data at national and international meetings. Results of the study will also be reported to the Sponsor and Funder, and will be available on their web site.

Expenses

If you agree to take part in this study we would cover all your travel expenses and we would arrange transport for you (by taxi) to come to the hospital and go home. We will also provide food and beverages for you and any family members who come with you for the testing sessions at the MR centre or at CARU. In addition, for some people and their family who are travelling from a distance it may be that they prefer to stay overnight in a hotel and in these cases we would cover all these expenses.

Personal information policy

If you decide to take part in the study, all information that you provide to us and the results of studies would be treated confidentially. It will be stored securely in locked cabinets or on password protected computer systems. Only people involved in the research study will have access to the information. We may retain the data in anonymised form to build a dataset of anonymised scan images that will be useful for future research studies and for the clinical reporting of scans. With your permission, we will also need to record your participation in Newcastle upon Tyne NHS Trust clinical notes. This will be done by authorised staff.

We will write to your General Practitioner (GP) and any specialists involved in your care informing them of your agreement to take part in this study with your permission.

Our tests are not routine clinical tests and are for research purposes only. However, if during the course of the study we note anything abnormal on any of the tests then we will tell you and your GP.

The NHS is trying to improve the quality of clinical and research standards. This is being achieved through 'clinical governance'. As part of this process, this study may be reviewed by a clinical governance team. Such a team would need to look at your records to make sure that the research was carried out in accordance with proper procedures.

What if there are any problems?

The NHS will provide indemnity for the study. If you have any concerns about any aspect of the way you have been approached or treated during the course of this study, the normal National Health Service complaints mechanisms will be available to you.

Who is organising and paying for the study?

The study is funded by the National Institute for Health Research. The research team are based at the Institute for Ageing and Health at Newcastle University.

Further information

If you would like further information please contact Dr John-Paul Taylor (in charge of the study), Alison Killen (research study co-ordinator) or any member of the research team at the Biomedical Research Building, Institute for Ageing and Health, Newcastle University, Campus for Ageing and Vitality, Newcastle upon Tyne, NE4 5PL (Telephone: 0191 248 1310).

What will happen next?

The next step will be a telephone call from one of the researchers. If you are interested in helping with the study, they will arrange to visit you at home. This will give you a chance to ask any questions about taking part before you make a decision. If you do decide to take part, the researcher will discuss a consent form with you and ask you to sign it. It is up to you to decide whether or not you want to take part. You do not have to give a reason if you do not want to be involved. Whatever you decide will have no effect on the care you receive now or in the future. If you change your mind you can withdraw from the study at any time without giving a reason. If you do withdraw, you can decide whether we can use any information you have already given us. You will be given a copy of this leaflet and a signed consent form to keep.

The research team should contact you in the next week or so. If, at any time, you need to get in touch with someone you can contact:

Alison Killen  **(0191) 248 1340**

John-Paul Taylor  **(0191) 248 1311**

Appendix 1.2 – Consent Form for Controls

**Biomedical Research Unit: Visual hallucinations: an EEG and non-invasive Stimulation
study
(BRU VEEG-Stim Study)**

I

of

Consent to taking part in the BRU VEEG-Stim Study.

**Please sign
and initial:**

I have read the information sheet giving details of this study; have been given a copy to keep and have had the opportunity to ask questions.

I understand that my participation is voluntary and I can withdraw consent at any time without giving any reason and without my medical care or legal rights being affected.

I understand that data collected during the study may be looked at in the monitoring of the research by clinical governance staff. I give permission for the researchers and clinical governance staff to have such access to my records.

I give permission for information concerning me to be held for 15 years by Newcastle University.

I understand that records will be confidential and will be stored securely on systems within the

NHS and University.

I agree to this research being recorded in the Newcastle upon Tyne NHS Trust clinical notes by authorised staff.

I give permission for my G.P. to be informed of my participation in this study.

I give permission that in the unlikely event that an abnormality is discovered my G.P. and I will be informed.

I consent for my data to be used in anonymised form to build a dataset of anonymised scan images that will be useful for future research studies and for the clinical reporting of scans.

I consent to taking part in the test-retest component of the study (if applicable)

Signed.....

Date.....

Consented by(signed)

Date.....

Print Name

Appendix 1.3 – Consent Form for Patients

**Biomedical Research Unit: Visual hallucinations: an EEG and non-invasive Stimulation
study
(BRU VEEG-Stim Study)**

I

of

consent to taking part in the BRU VEEG-Stim Study.

**Please sign
and initial:**

I have read the information sheet giving details of this study, have been given a copy to keep and have had the opportunity to ask questions.

I understand that my participation is voluntary and I can withdraw consent at any time without giving any reason and without my medical care or legal rights being affected.

I understand that any sections of my medical notes may be looked at and information taken to use in this research, or in research monitoring by clinical governance staff. I give permission for the researchers and clinical governance staff to have such access to my records.

I give permission for information concerning me to be held for 15 years by Newcastle University.

I understand that records will be confidential and will be stored securely on systems within the

NHS and University.

I give permission for my G.P. to be informed of my participation in this study.

I give permission that in the unlikely event that an abnormality is discovered my G.P.

and I will be informed.

In the possible event of my losing mental capacity to give informed consent during this study,

I wish it to be noted that I am minded to continue in the study.

I consent for my anonymised data to be used to build a dataset of anonymised scan images that will be useful for future research studies and for the clinical reporting of scans.

I consent for the study researchers to approach my family member/carer with regard to asking them to complete a number of carer-related questionnaires.

Signed.....

Date.....

Consented by (signed)

Date.....

Print Name

Appendix 1.4 – Consent Form for Carers

**Biomedical Research Unit: Visual hallucinations: an EEG and non-invasive Stimulation
study**

(BRU VEEG-Stim Study)

I

of

consent to taking part in the BRU VEEG-Stim study and completing questionnaires about my relative/dependent/friend.

**Please sign
and initial:**

I have read the information sheet giving details of this study, have been given a copy to keep and have had the opportunity to ask questions.

I understand that my participation is voluntary and I can withdraw consent at any time without giving any reason and without my medical care or legal rights or those of my relative/dependent/friend being affected.

I understand that data collected during the study may be looked at in the monitoring of the research by clinical governance staff. I give permission for such access to the information I have provided.

I give permission for the information I give to be held for 15 years by Newcastle University.

I understand that records will be confidential and will be stored securely on systems within the

NHS and University.

I consent for my data to be used in anonymised form in similar studies.

Signed.....

Date.....

Consented by (signed)

Date.....

Print Name

Appendix 2 – Phosphene Complexity Questionnaire

Average Phosphene Characteristics

Experimenter Copy

Participant code:

Date:

Responder?

Optimal Stimulation Site:

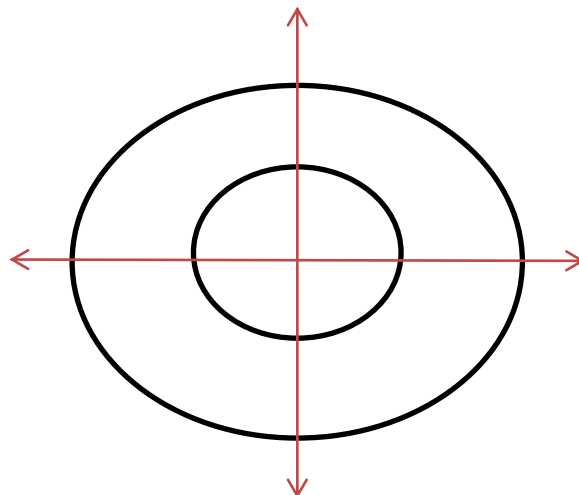
Threshold:

Subjective Reports? (If yes use separate sheet to detail):

Average Phenomenology

Q1. How would you describe the average size of the phosphenes that you reported?

Q2. Approximately where in your field of vision would you use to describe the placement of the phosphenes? Please use the diagram to help guide your answer:



Q3. Did you notice any movement of the phosphenes? For example, side-ways (e.g. left to right), vertically (e.g. up to down), spinning, trembling.

Q4. Over the course of the experiment what would you say was the main colour of the phosphenes? If the phosphene colour appeared to change, how would you describe this?

Q5. Did the phosphenes appear bright or dim? Please use the scale below to help with your answer.

Very Dim

Very Bright

1	2	3	4	5
---	---	---	---	---

Q6. Did the phosphenes appear to take on a particular shape?

Q7. If Q6 = Yes, Did the shape appear to change at all?

Q8. Did any of the phosphenes take on any of the following forms?

A person/face:

An animal:

A household object:

A complicated shape

Appendix 3 - Poster Presented at the British Neuroscience Association Meeting April 2015:
Reliability of ICA for the Removal of TMS artefacts in EEG

Towards a Gold-Standard for Combined TMS and EEG Data Pre-Processing: A critical examination of the effectiveness and reliability of a two tiered independent components analysis approach

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Background

- Combined TMS and EEG hold the potential to expand our understanding of cognitive processes.
- However, analysis of the EEG is hindered by significant artefacts caused by the TMS pulse.
- Although artefact limiting hardware exists they are not widely available, and rely upon removing a time window of data.
- One alternative approach is ICA which has been demonstrated as an effective offline solution to the problem (Korhonen et al, 2010/11; Rogasch et al, 2014; Mäki et al, 2011) although no attempt has been made to distribute a standard method for its use in this context.

Aim

- Assess the efficacy of a standardised protocol, by demonstrating the test-retest reliability of ICA for the removal of TMS induced EEG artefacts.

Methods

Participants

- A sample of six participants (18-82) were randomly selected from a larger cohort study (by an independent clinician) where all participants had previously received occipital cortex TMS whilst recording EEG (128 channel). Stimulation intensity was set using the individual's phosphene threshold.
- Analyses were conducted with the analyst blind to the participant demographics to avoid bias.

Event Related Potentials

- Trials were split into epochs of 2048ms (-1024:+1024ms) and baseline corrected using the period of -210:-10ms.
- Poor trials were removed after ICA cleaning to reduce the influence of extraneous artefacts.

Independent Components Analysis

- EEG Signals were decomposed using FASTICA and optimised to prevent overlearning (e.g. Korhonen et al, 2010). Components were classified by an experienced EEG analyst. ICA was performed at two stages (see figure 1).

Component Removal

- Temporal envelope of the component ERP's was computed. Components were then ranked in order of their contribution to the envelope, within a given window.

#1: Pulse Removal (-40:+40ms)

- Sharp changes in potential and characteristic decay artefacts (see figure 2).

#2: Common Artefacts (-200:+500ms)

- Sources of muscular artefacts, blinks, and line noise (50Hz).

Reliability

- Global field power (Lehman & Skrandies, 1980) was estimated at each stage in the process (pre-cleaning; one round of ICA; 2 rounds of ICA; completed ERP).
- To measure the effect of component removal on the EEG signal we recorded the following at each stage: percentage of components removed; early artefact amplitude (0-20ms); the number of peaks in the GFP.

Analysis

- We performed non-parametric comparisons of the reliability data at each stage of the cleaning within and between repetitions of the protocol.

Results and Conclusions

- Figure 3 demonstrates the inspection of the GFP at each stage of the process, and repeated on 3 separate occasions. Over time we see that the amplitude of the artefact period is significantly reduced (mean, 5.5 μV ; $\chi^2(11)= 58.432$, $p<0.05$), and that the peak structure of the GFP remains unchanged (mean, 3.68, sd, 0.76; $\chi^2(5)= 13.866$, $p=.240$).
- Additionally, this was achieved with no differences in the percentage of components removed (mean 12.4%; sd 3.2; $\chi^2(5)= 2.927$, $p=.711$).
- We have demonstrated that it is possible to reliably perform an effective removal of the mechanical and muscular artefacts induced by the TMS-evoked potential.
- This was performed without damaging the structure of the resulting ERP waveform. Despite the small sample size the outcome is such that the use of ICA to remove these artefacts can be standardised and confidently applied between subjects to elicit comparable outputs.
- We suggest that this methodology be considered as a baseline for the further refinement of approaches to the pre-processing of combined TMS-EEG data.

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**Appendix 4 – Individual Participant Global Field Power Peak Latencies used for the
TMS Evoked Potential Component Windowing**

Windows were defined as the global field power (GFP) peak latencies \pm 10ms.

Group	Participant Code	Global Field Power Peak Latency (ms)			
		Peak 1	Peak 2	Peak 3	Peak 4
<i>Controls</i>					
	veeg01	50.29	112.8	184.1	290.5
	veeg02	84.47	121.6	225.5	312
	veeg03*	47.36	96.19	156.7	286
	veeg04	46.39	100.1	168.9	225
	veeg20	70	128.9	176.3	262.7
	veeg23	97.66	162.6	245.6	364.7
	veeg24	38.09	70.31	128.9	197.8
	veeg25	80.08	119.6	165	223.6
	veeg26	50.29	122.6	206.5	279.8
	veeg27	38.57	101.1	194.8	255.4
	veeg29	65	119.1	201.2	305.7
	veeg30	42.97	107.9	172.9	307.1
	veeg31	56.15	128.4	178.7	235.8
	veeg32	54.2	124	172.4	231.9
	veeg33	46.39	100.6	172.4	213.4
	veeg35	46.88	110	197.3	324.2
<i>PDD VH</i>					
	veeg05	41.99	109.9	202.1	274.4
	veeg06	54.2	109.4	168	323.2
	veeg07	93	150.9	225.6	317.9
	veeg09	46.88	104	167.5	217.8
	veeg12	59.08	127.9	205.1	339.4
	veeg13	75.68	116.7	179.7	301.8
	veeg14	58.11	132.3	189.9	258.3
	veeg16*	115.2	207	292.5	360.8
	veeg19	90.33	145.5	229.5	339.8
	veeg22	66.41	112.8	177.7	293
	veeg39	50.29	98.63	181.6	286.1
	veeg41	35	116	213.4	308.1
<i>PDD NVH</i>					
	veeg10	60.06	131.3	187.5	282.2
	veeg15*	42.97	97.66	214.8	270
	veeg34	48.34	104	176.8	237.7
	veeg37	34.67	64.94	127.9	214.8
	veeg40	70.31	108.4	177.2	320.8
	veeg43	68.85	120.1	179.7	256.3

* excluded from main analyses

Appendix 5 – List of Publications

It is noted that some portions of the information contained within this document have been adapted from original research articles and conference submissions by the author. These can be found in the following sections:

Introduction (Chapter 1)

Murphy, N.R.E., Graziadio, S. and J.P., T. (2015) 'Chapter 8: EEG and transcranial magnetic stimulation', in Collerton, D., Mosimann, U. and Perry, E. (eds.) *The Neuroscience of Visual Hallucinations*. United Kingdom: Wiley Publishing.

Methods (Chapter 3)

Murphy, N.R.E., Tomasevic, L., Graziadio, S., Peraza, L., Rochester, L. and Taylor, J.P. (2015) 'Towards a Gold-Standard for Combined TMS and EEG Data Pre-Processing: A critical examination of the effectiveness and reliability of a two tiered independent components analysis approach.' *British Neuroscience Association meeting*. Edinburgh, 12/04/2015.

Visual Evoked Potentials (Chapter 5)

Murphy, N.R.E., Killen, A., Graziadio, S., Peraza, L., Firbank, M., Baker, M., Elder, G., Thomas, A., McKeith, I., Rochester, L. and Taylor, J.P. (2015) 'Early bottom-up visual information processing in hallucinating patients with Parkinson's disease with dementia: a preliminary visual evoked potential study', *Am J Neurodegener Dis* 4((Supplementary Issue 1)), pp. 1-178.

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