Investigating attentional function and cognitive fluctuations in Lewy body dementia

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Abstract

Objective:

Lewy body dementias (LBD), which include dementia with Lewy bodies (DLB) and Parkinson's disease with dementia (PDD), are characterised by attentional dysfunction and fluctuating cognition. The underlying aetiology of these clinical features is poorly understood, yet such knowledge is essential for developing effective management strategies. The aim of this project was to determine the specific facets of attention affected in LBD patients, and to use high-density electroencephalography (EEG) to delineate the underlying pathophysiology and how this relates to cognitive fluctuations.

Methods:

Attentional network efficiency was investigated in LBD patients (n = 32), Alzheimer's disease (AD) patients (n = 27), and age-matched healthy controls (n = 21) by using a modified version of the Attention Network Test (ANT). The ANT, a visual attention task, probes the efficiency of three anatomically defined attentional networks: alerting, orienting and executive conflict. Participants completed the ANT whilst undergoing EEG recordings (128 channels). In a subsample of the participants (22 DLB, 24 AD, 19 controls), time-frequency wavelet analyses were conducted to investigate event-related spectral perturbations (ERSP), between 4-90 Hz, in the 500 ms post-stimuli presentation. Attentional network ERSP was calculated by contrasting the oscillatory reactivity following relevant stimuli.

Results:

Overall mean reaction time was slower in the dementia groups (AD and LBD) relative to the controls, and the LBD group were slower than the AD group. Behaviourally, there were no group differences regarding the orienting effect. However, both dementia groups exhibited reduced executive conflict processing efficiency, and a lack of an alerting effect. Electrophysiologically, the DLB group exhibited a profound lack of post-stimulus oscillatory reactivity below 30 Hz, irrespective of stimulus condition. For the alerting network, the DLB group exhibited attenuated reactivity in the lower frequencies (< 30 Hz); in the theta range (4-7 Hz) the controls and AD group showed global synchronisation (across all regions), peaking at approximately 300 ms, which was absent in the DLB group. Lack of DLB theta synchronisation between 200-450 ms over the right parietal cortex was associated with a

higher total score on the Clinical Assessment of Fluctuation scale. Orienting and executive conflict network reactivity was comparable across all groups; primarily intermittent synchronisation, of reduced power relative to the alerting network, diffuse across the time and frequency domains in all regions.

Conclusions:

Attenuated global oscillatory reactivity in the DLB group specific to the alerting network (the network associated with the ability to maintain an alert state) is indicative of this fractionated aspect of attention being differentially affected in the DLB patients relative to the AD and control groups. Lack of theta reactivity in the parietal regions may contribute to the underlying pathophysiology of cognitive fluctuations in DLB.

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Abbreviations

AD: Alzheimer's disease

ANOVA: Analysis of variance

ANT: Attention Network Test

CAF: Clinician Assessment of Fluctuations scale

CAMCOG: Cambridge Cognitive Examination

CATFieLD (study): Cognitive and AttenTional Function in Lewy body Disease

CRB: Channel reactivity-based analysis

dB: Decibel

df: Degrees of freedom

DLB: Dementia with Lewy bodies

DMN: Default mode network

EEG: Electroencephalography

ERD: Event-related desynchronisation

ERP: Event-related potential

ERS: Event-related synchronisation

ERSP: Event-related spectral perturbation

fMRI: Functional magnetic resonance imaging

Hz: Hertz

IAF: Individual alpha frequency

ICA: Independent component analysis

IIR: Infinite impulse response

LBD: Lewy body dementia

MATLAB: Matrix Laboratory computer package

MFS: Mayo Clinic Fluctuations Scale

MMSE: Mini Mental State Examination

ms: Milliseconds

NPI: Neuropsychiatric Inventory

ODFAS: One Day Fluctuation Assessment Scale

PD: Parkinson's disease

PDD: Parkinson's disease with dementia

PSD: Power spectral density

RT: Reaction time

SD: Standard deviation

SE: Standard error

SOA: Stimulus onset asynchrony

SPSS: Statistical Package for Social Sciences

UPDRS: Unified Parkinson's disease rating scale

μV: Microvolt

Chapter 1 . Introduction

1.1 Lewy body dementia

Lewy body dementia (LBD), encompassing dementia with Lewy bodies (DLB) and Parkinson's disease with dementia (PDD), is now recognised as the second most common form of degenerative dementia after Alzheimer's disease (Vann Jones & O'Brien, 2014). Approximately 10-15 % of dementia cases demonstrate Lewy body pathology at autopsy (McKeith, 2006). LBD patients therefore represent an important disease group in older age, with a significant and corresponding impact upon health and society.

1.1.1 Dementia with Lewy bodies versus Parkinson's disease with dementia

DLB and PDD are differentiated from each other according to the onset of dementia relative to parkinsonism; DLB is diagnosed if the onset is less than one year after the onset of parkinsonism, PDD if more than one year elapses prior to dementia onset (McKeith, 2006). Whilst differences exist in terms of the timing of parkinsonism relative to the cognitive impairment, it is likely that both conditions represent different points on a Lewy body disease spectrum, with the underlying and common clinical neuropathology being the aggregation of alpha-synuclein (Francis, 2009) (see section 1.1.3). However, the relationship between clinical manifestations and associated neuropathological changes has not been consistent, and how to best diagnose and treat LBD is only beginning to be elucidated.

1.1.2 Clinical features

Core clinical features associated with LBD include fluctuations in cognition and attention, spontaneous motor features of parkinsonism, and recurrent complex visual hallucinations; these are the core diagnostic criteria for a diagnosis of probable DLB (McKeith, 2006). Further supportive features of the disease include autonomic dysfunction, syncope, repeated falls, rapid eye movement sleep behaviour disorder (RBD), neuroleptic sensitivity, delusions and depression (McKeith, 2006). Cognitively, LBD patients often

exhibit marked deficits in executive functioning, as well as visuospatial and visuoperceptual deficits (Mollenhauer et al., 2010), and thus LBD is a highly debilitating condition.

Whilst there is a degree of overlap between the cognitive phenotype of LBD and that of Alzheimer's disease (AD), LBD and AD patients tend to be comparable in terms of global cognitive functioning assessment scores when comparing individuals of similar disease duration (i.e. Mini Mental State Examination scores) (McKeith et al, 2003). However, whilst DLB patients tend to exhibit less severe impairments in episodic memory relative to AD patients (Calderon et al., 2001; Hamilton et al., 2004; Walker et al., 1997), AD patients have consistently been shown to outperform DLB patients on tasks of visuoperception and attention (Collerton et al., 2003; Hamilton et al., 2004; Hansen et al., 1990) (see section 1.3.1. for details of attentional dysfunction in LBD), reflecting divergences in cognitive profile and thus underlying aetiologies between the two conditions.

1.1.3 Neuropathology of LBD

The underlying neuropathology of LBD is the presence of Lewy bodies at autopsy: intraneuronal cytoplasmic inclusions comprising aggregates of alpha-synuclein (a pre-synaptic protein) and ubiquitin (a heat shock protein associated with protein degradation) (Figure 1.1).

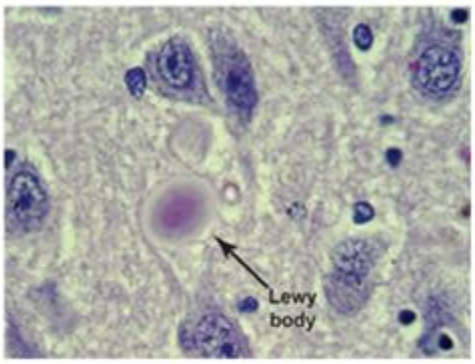


Figure 1.1. A brainstem Lewy body, comprising a hyaline core and a pale halo (Dickson, 2006).

Immunohistochemical studies, using alpha-synuclein antibodies, have shown that, typically, in the early stages of the disease (particularly in Parkinson's disease (PD) / PDD), Lewy bodies are typically evident in the brainstem; these proliferate as the disease progresses, and cortical Lewy bodies are common in the latter stages of the disease (Figure 1.2). Braak et al.

(2003) proposed a staging for progressive alpha-synuclein accumulation, with Lewy body pathology initiating in the dorsal motor nucleus of the vagus in the medulla oblongata, spreading rostrally to the pons and midbrain, followed by the limbic system, and finally to the neocortex (Braak et al., 2003). This Braak staging was proposed as a means of documenting the accumulation of Lewy body pathology in PD. Whilst this caudo-rostral Lewy body accumulation tends to be evident in PDD patients, this is not always the case in DLB patients, and thus the extent to which the Braak staging hypothesis is applicable to DLB is yet to be elucidated (Walker et al., 2015).

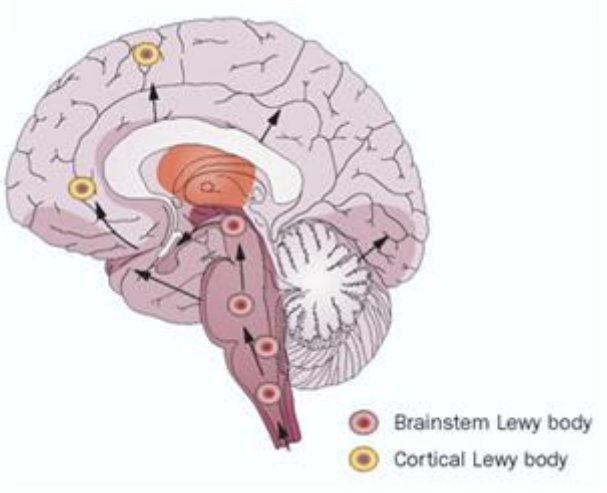


Figure 1.2. In the early stages of the disease Lewy bodies are typically present in the brainstem, as the disease progresses cortical Lewy bodies are also evident (Obeso et al., 2010).

Subcortically, in LBD patients, structures commonly affected by Lewy body pathology include: the amygdala, lateral and posterior hypothalamus, and the brainstem reticular formation (Dickson, 2006). Although Lewy bodies are not common in the thalamus or basal ganglia, Lewy neutrites, which like Lewy bodies contain aggregates of alpha-synuclein, are often present in these structures (Dickson, 2006). Cortical Lewy bodies, usually present in non-pyramidal neurons of lower cortical layers (Dickson, 2006), are often evident in the temporal and frontal association areas, and limbic cortices; they have been found to be particularly abundant in the insular cortex and cingulate and parahippocampal gyri (Hamilton, 2000). Although more extensive striatal Lewy body pathology has been observed in DLB relative to PDD patients (Jellinger & Attems, 2006), the neuropathological features of the two conditions are generally considered to be similar (Lippa et al., 2007; Walker et al., 2015).

In addition to Lewy bodies, LBD cases often show evidence of regional neuronal loss (particularly in the brainstem and nucleus basalis of Meynert), and spongiform change; neuropil microvacuolation which is a neuropathological feature of transmissible spongiform encephalopathies; however in LBD spongiform change is often restricted to the amygdala, and limbic and temporal cortices (Dickson, 2006).

Many LBD patients have concomitant AD pathology at autopsy; the presence of neuritic plaques (extracellular deposits of amyloid-beta protein) and neurofibrillary tangles (aggregates of hyperphosphorylated tau protein within neuronal cell bodies). Although amyloid-beta pathology is often quite marked in DLB (Donaghy et al., 2015; Mak et al., 2014), usually tau pathology is relatively low unless the patient exhibits concurrent AD (Dickson, 2006). Cortical amyloid-beta pathology has been shown to be greater in DLB patients relative to PDD patients (Donaghy et al., 2015), and greater striatal amyloid-beta deposition has been found to differentiate DLB from PDD patients (Halliday et al., 2011). The clinical syndrome of DLB is related to the severity of Lewy body pathology, but inversely related to the severity of concurrent AD tau pathology (McKeith et al., 2005).

Neuropathological correlates of LBD cognitive features

The distribution and density of cortical Lewy bodies has been found to correlate with cognitive features of LBD; when Lewy body pathology is restricted to the brainstem patients tend to exhibit parkinsonism without cognitive dysfunction (Dickson, 2006; Harding & Halliday, 2001). With regard to visual hallucinations, Lewy body density in the parahippocampal gyrus and inferior temporal cortex has been found to associate with the presence of well-formed visual hallucinations in DLB patients (Harding et al., 2002).

Given that cholinergic dysfunction in LBD is substantially greater than in AD (Ballard et al., 2013) it is postulated that reduced integrity of the cholinergic system in LBD may be a contributory factor underlying the aetiology of cognitive features of the disease, in particular, the manifestation of cognitive fluctuations and attentional dysfunction. In DLB patients, it is well established that there is a marked loss of basal forebrain cholinergic neurones (which have widespread projections to the neocortex) compared to AD patients (Perry et al., 1993); furthermore, nicotinic receptor binding in DLB patients appears to be associated with disturbances of consciousness (Ballard et al., 2002b; Perry et al., 1999). Pharmacological evidence has demonstrated that anticholinergic drugs can induce a symptom profile of altered

arousal (Perry et al., 1999) that is similar to fluctuating cognition in DLB and, by contrast, cholinesterase inhibitors significantly improve the fluctuating cognition in DLB and PDD (McKeith et al., 2000c). However, it should also be recognised that it is likely that other cortical systems responsible for arousal and attention may be compromised and contribute to the development of fluctuating cognition. In particular, it has been posited that non-cholinergic systems including dopamine (particularly in PDD) and noradrenergic systems, as well as structures that mediate arousal and circadian function such as the hypothalamus and midbrain, may have a role (Dickson et al., 1987; Ferman et al., 2004).

1.2 Attention

Attentional dysfunction, which is a characteristic feature of LBD, is discussed in detail in section 1.3. Given that attention is a broad concept, the purpose of this section (prior to discussing attention in the context of LBD) is to provide a brief overview of some of the models which have been devised in an attempt to conceptualise the notion of attention; from purely theoretical cognitive models, to a more neuroscientific approach.

1.2.1 Theories of attention

'Everyone knows what attention is. It is taking possession of the mind, in clear and vivid form, of one out of what seems several simultaneously possible objects or trains of thought. Focalization, concentration of consciousness are of its essence.'
(William James, psychologist-1890)

Since early definitions of attention dating back to the 1800s (see above), the concept of attention has generated great interest amongst psychologists, and has emerged as one of the most prominent fields of research in modern cognitive psychology. There has been extensive debate as to how best define and study attention; a plethora of attentional theories have been proposed as a result of studying various aspects of attention, with particular focus on visual and auditory domains. An in depth discussion encompassing all of the suggested attentional models is beyond the scope of this chapter; however there is a broad consensus that attention involves the selection of specific information for further processing, whilst inhibiting other information from receiving further processing.

In the latter half of the twentieth century attentional research was dominated by 'Bottleneck' theories of attention; whereby it is postulated that attentional resources are limited and thus a necessary filtering process takes place (irrelevant stimuli are filtered out). Several bottleneck models have been suggested, although there are disparities between the models with regard to the extent to which irrelevant stimuli are filtered out, and the processing stage at which this filtering occurs. One of the most influential bottleneck models is Broadbent's filter model of attention (Broadbent, 1958), which suggests that during an early pre-attentive stage in information processing, stimuli are filtered (selected to be attended to) according to their basic features (physical characteristics); stimuli with comparable features are attended to and processed for meaning, whilst other stimuli are filtered out. Treisman (1964) devised an attenuation theory of attention which, comparable to Broadbent's theory, suggests that stimuli are filtered according to their physical characteristics, however, in contrast this theory suggests that irrelevant stimuli are attenuated by the filter as opposed to being eliminated entirely (i.e. unattended stimuli are processed to a lesser extent than attended stimuli). This model accounts for the ability to switch attention to an unattended stimulus if it is meaningful, and thus accounts for a degree of semantic processing of unattended stimuli. Deutsch and Deutsch (1963) proposed a late selection model which suggests that all stimuli undergo analysis for meaning prior to selection of relevant information (stimuli to be attended to); selection of information is influenced by the relevance of the stimuli at the time of processing.

Towards the end of the twentieth century, the development and widespread availability of neuroimaging techniques resulted in a shift in attention research towards a more neuroscientific approach. Cognitive neuroscience has enabled the neural correlates of attentional processes to be studied, thus resulting in the emergence of tangible neuroanatomical models of attention. One of the most prominent neurocognitive models in recent attention research, the attentional network model, is discussed in the following section.

1.2.2 Attentional networks

Posner and colleagues (Fan et al., 2002; Posner & Petersen, 1990) have suggested that attention can be modelled as having three functionally inter-related but anatomically distinct components: alerting, orienting, and executive control.

Alerting

Alerting is the ability to achieve and maintain an alert state, and has been found to be associated with prefrontal and parietal activation of the right hemisphere (Posner & Petersen, 1990). Widespread cortical noradrenergic projections from the locus coeruleus are postulated to have an integral role in the modulation of the alerting network (Noudoost & Moore, 2011).

Orienting

Orienting involves the selection of information from sensory input. The efficiency of this network can be assessed by the shift of attention which occurs due to the presentation of stimuli in a previously cued location in space (Fan et al., 2005). Orienting of attention following the presentation of a cue has been found to be associated with activation of the pulvinar, frontal eye fields, superior colliculus, prefrontal and parietal regions (notably the superior parietal lobe) (Corbetta et al., 2000). Cholinergic system integrity, in particular the basal forebrain cholinergic system, has been found to have a crucial role in regulating the orienting network (Fan et al., 2005).

Executive control

Executive control of attention involves the resolution of conflict amongst sensory inputs. Flanker tasks, which involve elements of conflict, are routinely used to investigate the efficiency of this network. Regions associated with executive functioning have been found to be widely dispersed throughout the brain (Posner & Petersen, 1990), however frontal and parietal regions, and the anterior cingulate have consistently been shown have a modulatory role in executive control of attention (Fan et al., 2001). Furthermore, both the dopaminergic and cholinergic systems have been found to have an integral role in prefrontal mediated executive control (Noudoost & Moore, 2011).

The efficiency of the three attentional components (or attentional networks as Posner and colleagues refer to them) can be assessed using the Attention Network Test (ANT); an elegant visual attention task devised by Fan et al. (2002). The ANT combines elements of the Erikson flanker task (Eriksen & Eriksen, 1974) and the Posner cueing paradigm (Posner & Petersen, 1990) to form a single reaction time task which is designed to probe the efficiency of the three attentional networks. The ANT has been used successfully in imaging and

electrophysiology studies (Fan et al., 2007; Fan et al., 2005) to demonstrate, and independently delineate, the different attentional components of alerting, orienting and executive function. The fractionation of attention into the three components, coupled with the task simplicity, renders the ANT an ideal task to investigate disease-specific attentional deficits in clinical populations, particularly dementia patients. Attentional network efficiency in relation to dementia cohorts is discussed in section 1.5.

1.3 Attentional dysfunction in LBD

LBD patients exhibit attentional deficits and variability in their levels of attention and of arousal; typically referred to as 'cognitive fluctuations' (Lee et al., 2012). Both cognitive fluctuations and attentional deficits have a major impact on activities of daily living (Bronnick et al., 2006), and there is evidence to suggest that they are likely to have a significant role in the formation of the distressing visual hallucinations that frequently accompany LBD (Collerton et al., 2005). Furthermore, in PD patients such cognitive impairments have been found to contribute to caregiver distress (Aarsland et al., 1999) and nursing home placement (Aarsland et al., 2000).

1.3.1 Attentional dysfunction

As discussed in section 1.1.2, whilst there is a degree of overlap in the cognitive phenotype of DLB and AD, there is a dissociable pattern between the two diagnoses in terms of executive and attentional functioning. Specifically, neuropsychological studies in DLB have noted deficits in attentional function ranging from simple processing speed through to complex attentional tasks requiring significant executive input. For example, relative to AD patients, DLB patients have been found to perform worse on executive function tasks such as the digit span subset of the WAIS- R (Hansen et al., 1990) (a measure of cognitive control), and tasks of selective attention such as the Cancellation Test (Noe et al., 2004). In PD patients, attentional dysfunction has been found to be associated with poorer quality of life (Lawson et al., 2014), and has been shown to be predictive of conversion from PD to PDD (Taylor et al., 2008).

1.3.2 Cognitive fluctuations

Fluctuating cognition is a core diagnostic feature of LBD, affecting approximately 90 % of DLB patients (McKeith, 2006) and 29 % of PDD patients (Ballard et al., 2002a). Clinically, patients experience frequent interruptions in awareness which are often associated with transient episodes of confusion and communicative difficulties. These fluctuations appear to be qualitatively distinct from the less frequently seen fluctuations in other dementias such as AD (McKeith, 2006). It has been postulated that these fluctuations are internally driven as remission to near-normal cognitive functioning can occur in the absence of external environmental triggers (Bradshaw et al., 2004). DLB patients have also been found to exhibit more severe fluctuations in attention relative to AD patients, with fluctuations in the latter more typically suggested to arise as a result of increasing environmental demands (Bradshaw et al., 2004).

1.3.3 Aetiology of attentional dysfunction and fluctuating cognition

As there is significant overlap in the clinical phenotype of DLB and AD, clarification regarding the aetiology of the attentional deficits and cognitive fluctuations associated with DLB could prove invaluable in aiding the differential diagnosis of the two conditions, and ultimately developing more effective symptom management strategies.

As discussed in section 1.1.3, dysfunction of the basal forebrain cholinergic system has been suggested to be a major contributory factor underlying the fluctuating cognition associated with LBD. Furthermore, in DLB patients microstructural damage in thalamic regions projecting to the pre-frontal and parieto-occipital cortices has been observed (Delli Pizzi et al., 2014a), and cholinergic imbalance (tCho/tCr increase) in the thalamus has been found to correlate with the severity of cognitive fluctuations (Delli Pizzi et al., 2014b), therefore it is postulated that reduced integrity of the cortio-thalamic system may be a contributory factor underlying attentional fluctuations associated with LBD. It has also been suggested that the greater severity of executive and attentional impairments in DLB patients relative to AD patients may in part be due to fronto-subcortical dysfunction; it is postulated that Lewy body pathology in the association areas of the frontal lobe, and pathology of the subcortical structures such as the substantia nigra, interrupts dopaminergic projections to the striatum (Salmon & Hamilton, 2006).

Neuroimaging studies, in particular functional magnetic resonance imaging (fMRI) studies, have been conducted in order to investigate neural correlates of attentional fluctuations. Weissman et al. (2006) showed in an fMRI study of young healthy adults that there was less activity pre-stimulus in anterior cingulate and right prefrontal areas during attentional lapses, and less deactivation of the default mode network (DMN; a measure of resting cognitive state, DMN deactivation is linked with attentional demand); recovery from these lapses was associated with increased stimulus-associated activity in right frontal and temporal/parietal regions. From this, Weissman et al. (2006) concluded that during attentional lapses the frontal network is unable to adequately bias the sensory cortices (e.g. visual system) via top-down processing, resulting in a failure to optimally attend to incoming stimuli. It could be argued that similar processes, albeit magnified and related to impaired connectivity between frontal and sensory areas, could contribute to the attentional fluctuations seen in LBD. However functional imaging of attentional function in LBD is very limited and the findings are not clear. One fMRI study demonstrated a reduction in the amount of DMN deactivation during motion and colour tasks in DLB patients relative to controls (Sauer et al., 2006). In contrast, in a recent fMRI attentional network study in which participants completed the ANT (see section 1.5), Firbank et al. (2015) reported greater DMN deactivation in LBD patients relative to controls in response to the presentation of task stimuli. However, in a resting state fMRI study Franciotti et al. (2013) found DMN activity in DLB patients to be comparable to controls, although they did report reduced right hemisphere functional connectivity between frontal and parietal regions in DLB patients, which correlated with cognitive fluctuation severity.

In addition to neuroimaging, neurophysiological techniques have potential to provide an insight into the aetiology of attentional dysfunction and cognitive fluctuations in LBD. Numerous electrophysiological studies have been conducted using LBD cohorts; these are discussed in the following section, with consideration as to how the findings relate to cognitive fluctuations and attentional dysfunction.

1.4 Electrophysiology of LBD

Neurophysiological techniques, particularly clinical electroencephalography (EEG), were regularly used in dementia diagnosis. However due to the development and ubiquity of neuroimaging in the diagnosis of dementia, the use of neurophysiology has somewhat fallen out of favour. Nevertheless it is important to acknowledge the value of neurophysiological

studies in dementia research: techniques such as EEG offer greater temporal resolution and are relatively inexpensive in comparison to many neuroimaging counterparts. Furthermore, with the development of new methodologies and analysis techniques, neurophysiology studies have the potential to provide insights into the underlying pathophysiology of the characteristic cognitive fluctuations and attentional deficits associated with the condition.

1.4.1 Neurophysiological techniques used to study LBD

Studies of LBD cohorts have employed a range of neurophysiological techniques including: EEG, magnetoencephalography (MEG), transcranial magnetic stimulation (TMS), electromyography (EMG), and blink reflex. For a detailed review of the various techniques used to study the neurophysiology of LBD, and the utility of such techniques for identifying potential biomarkers of LBD, please see appendix A. Of all of the various neurophysiological approaches, EEG (see section 1.4.2) is by far the most commonly used technique to study LBD patients. One of the main advantages of EEG is it has excellent temporal resolution. This is particularly pertinent when investigating the neurophysiology associated with LBD features; in particular, investigating cognitive and attentional fluctuations over time resolutions of subsecond to millisecond range.

1.4.2 Electroencephalography (EEG)

EEG is a non-invasive technique used to record neuronal activity of the brain. Electrodes (often embedded into a cap) are placed on the scalp surface and an electro-gel is used to bridge the conductance gap between the electrode and the scalp. EEG measures variation in voltage over time; the potential difference between two electrodes is recorded. The synchronous activity of tens of thousands of neurons is required in order to generate the EEG signal; the signal is attenuated by the scalp and is usually less than 100 μV. The main source of the EEG signal is the summed activity of the apical dendrites of the cortical pyramidal neurons (excitatory and inhibitory postsynaptic potentials). Postsynaptic potentials have a longer duration (tens of milliseconds) relative to action potentials (approximately 1 ms), and therefore it is the activity of postsynaptic potentials which is more likely to be summed and contribute to the signal recorded at the scalp. Apical dendrites are aligned parallel to each other and perpendicular to the cortical surface (Figure 1.3), and are thus

optimally oriented to generate summed activity detectable by scalp electrodes (Niedermeyer & da Silva, 2005).

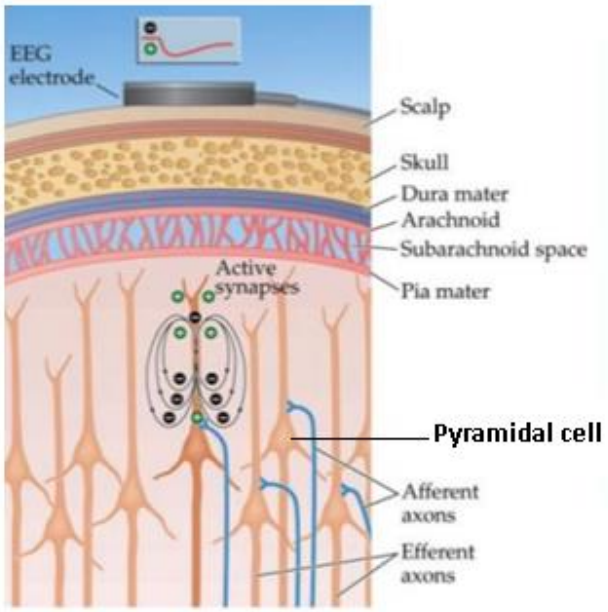


Figure 1.3 . The alignment of cortical pyramidal cells in relation to the scalp. Figure adapted from Niedermeyer & da Silva (2005). Pyramidal neurons have several basal dendrites, and a long apical dendrite (emerging from the apex of the cell body) which ascends to the cortical surface. The postsynaptic potentials of the apical dendrites sum together to form the signal recorded by the scalp electrode.

Cortical pyramidal neurons are innervated by direct projections from the thalamus and other cortical areas. In addition, the pyramidal neurons also form synapses with interneurons in the cortex which, in turn, are innervated by thalamocortical and corticocortical fibres. Specific thalamocortical projections (topographic pathways which relay sensory information to the corresponding cortical region) innervate pyramidal cells in deep cortical layers, whereas non-specific thalamocortical afferents (which are less topographic) form synapses with pyramidal cells in the superficial cortex (Kirschstein & Kohling, 2009). It is activity of the non-specific thalamocortical afferents projecting to the superficial pyramidal cells which are the main source of EEG signal.

Due to the perpendicular orientation of pyramidal cell dendrites with respect to the cortical surface, they form excellent dipoles (Kirschstein & Kohling, 2009). The polarity of the dipole is determined by the cortical depth of the synaptic input to the apical dendrite. Positive and negative scalp potentials (deflections in the EEG signal) are the result of both excitatory and inhibitory synaptic inputs; positive potentials are generated by deep cortical

excitatory or superficial inhibitory inputs, whereas negative potentials are generated by deep inhibitory or superficial excitatory synaptic inputs (Kirschstein & Kohling, 2009).

EEG recordings can be conducted either whilst the participant is at rest, or whilst the individual is presented with a stimulus or performs a task. Resting state EEG recordings, whereby there is an absence of a stimulus, are typically conducted with the participants' eyes closed. Numerous analysis approaches have been developed to analyse both resting state and task-related EEG data, and a wide range of techniques have been use to investigate the pathophysiology of LBD. A common analysis approach, particularly when analysing resting state EEG, is to examine frequency bands of interest (most commonly investigated frequency bands are delta, theta, alpha, beta and gamma), in order to investigate, for example, the power within a specific frequency band, which can be compared between patient groups and healthy controls. With regard to task-related activity, this is often examined in the time domain by analysing event-related potentials (ERPs); positive or negative waveforms (deflections in the EEG signal) which are evident following the presentation of stimuli. ERPs are defined in accordance with the polarity of the waveform (i.e. positive or negative), and the latency at which it occurs following stimulus presentation (in milliseconds). For example, the P300 ERP component is a positive waveform, evident approximately 300 ms following the presentation of a stimulus (Luck, 2005). ERP features such as amplitude and latency have been found to be associated with a variety of cognitive processes, and therefore ERP studies in LBD cohorts may provide an insight into the neurophysiology of attentional dysfunction in LBD.

1.4.3 EEG and LBD

As discussed in section 1.3.3, it is postulated that reduced integrity of the cortico-thalamic system contributes to the cognitive fluctuations observable in LBD patients. Given that the cortico-thalamic system has a pivotal role in the generation of cortical synchronous oscillatory activity (Timofeev et al., 2012), EEG studies of LBD cohorts have potential to provide an insight into the neurophysiology underlying the fluctuating cognition and attentional dysfunction associated with the disease.

Resting state EEG and LBD

An established feature of resting state EEG activity in DLB patients is the presence of posterior (temporal) transient slow or sharp waves (Barber et al., 2000; Briel et al., 1999); this is specified in the DLB diagnostic criteria as a supportive feature of the condition (McKeith et al., 2005). Increased posterior slow-wave activity has been observed in LBD patients relative to healthy controls and AD patients (Bonanni et al., 2008; Briel et al., 1999; Calzetti et al., 2002; Fernandez-Torre et al., 2007; Roks et al., 2008). Whilst DLB patients tend to exhibit aberrant activity in posterior regions, AD patients have been found to exhibit atypical activity in temporal regions (Bonanni et al., 2010; Bonanni et al., 2008), which is indicative of topographical differences between DLB and AD patients with regard to aberrant EEG activity. Furthermore, increased variability of low frequency posterior activity (on a second by second basis) in DLB patients relative to AD patients and controls has been found to positively correlate with the severity of clinically assessed cognitive fluctuations (Bonanni et al., 2008; Walker et al., 2000c).

Given that the cortico-thalamic system has a modulatory role on the synchronisation of cortical activity (Timofeev et al., 2012), and microstructural damage in thalamic regions projecting to the pre-frontal and parieto-occipital cortices has been observed in DLB patients (Delli Pizzi et al., 2014a), it has been suggested that the presence of increased slow wave activity in DLB patients may be due to reduced integrity of the cortico-thalamic system (Babiloni et al., 2011). Furthermore, there are substantial interactions between the thalamo-cortical pathways and the basal forebrain cholinergic system, therefore it is postulated that cholinergic system dysfunction may be an underlying factor in the aberrant cortical activity observed in DLB patients. There is evidence to suggest cholinergic medication has a modulatory effect on cortical activity; in healthy individuals administration of the cholinergic antagonist scopolamine has been found to result in abnormal activity in the alpha and theta frequency bands (Osipova et al, 2003). Clinically, cholinesterase inhibitors enhance attentional function and alertness (McKeith et al., 2000a; Wesnes et al., 2005), and in AD patients a reduction in delta and theta activity has been observed following cholinesterase inhibitor treatment, along with increased alpha activity and enhanced cognitive functioning (Babiloni et al., 2013). Given the association between atypical slow wave activity in DLB and severity of cognitive fluctuations (Bonanni et al., 2008; Walker et al., 2000c), along with cholinergic imbalance (tCho/tCr increase) in the thalamus of DLB patients which has been found to correlate with cognitive fluctuation severity (Delli Pizzi et al., 2014b), it is possible

that atypical cortical activity due to reduced integrity of the cortico-thalamic and cholinergic systems may contribute to the manifestation of cognitive fluctuations in LBD patients.

Resting state EEG coherence has also been studied in DLB patients, which is a measure indicative of functional cortical connectivity, and in the context of DLB a measure which may highlight modulatory effects of cholinergic dysfunction (Adler et al., 2003). Andersson et al. (2008) investigated coherence between four regions (left anterior, right anterior, left posterior and right posterior) in DLB patients. Relative to controls, DLB patients exhibited greater extended coherence (average coherence between all regions) in the delta frequency band, but reduced extended alpha coherence (Andersson et al., 2008). In a comparable study, Kai and colleagues reported dissimilarities between DLB and AD patients with regard to fronto-temporocentral delta and theta intrahemispheric coherence values, and temporo-centro-parieto-occipital beta coherence values; the authors speculated that this may be due to greater cholinergic dysfunction in the DLB patients (Kai et al., 2005).

In summary, the greater temporal resolution afforded by EEG compared to neuroimaging methods, such as blood oxygen level dependent (BOLD) fMRI, may offer better aetiological perspectives into the fluctuating perturbations in brain networks that occur in LBD.

Event-related potential studies in LBD

Whilst the existing literature pertaining to ERPs in LBD patients is relatively sparse, several studies have demonstrated that atypical ERPs are a common feature of LBD (Bonanni et al., 2010; Kurita et al., 2010; Perriol et al., 2005; Pugnetti et al., 2010). ERP studies of LBD patients may have important implications for understanding the pathophysiology of the condition; for example, by providing a greater understanding of the temporal processes underlying attentional dysfunction (Brønnick et al., 2010; Kurita et al., 2010).

A study conducted by Bonanni and colleagues, using an auditory oddball paradigm, demonstrated that the P300 component over parietal regions in DLB patients had reduced amplitude and greater latency relative to AD patients (Bonanni et al., 2010). In addition, the P300 anterior-to-posterior amplitude gradient was inverted in the DLB patients; there was a greater amplitude in frontal regions and smaller amplitude in posterior regions in DLB patients relative to AD patients and controls. Given that DLB is characterised by early frontal lobe involvement and executive dysfunction (Dodel et al., 2008), this reversed amplitude

gradient may initially seem counterintuitive (i.e. reduced frontal amplitudes may be expected in DLB). However, the DLB patients also exhibited delayed P300 latency in anterior regions relative to the AD patients, which the authors suggested is compatible with the role of the frontal lobe in the manifestation of the DLB cognitive phenotype. In addition, the delayed P300 latency and atypical anterior-to-posterior amplitude gradient in the DLB patients correlated with the severity of clinically assessed cognitive fluctuations, therefore these P300 parameters may serve as useful objective electrophysiological biomarkers of cognitive fluctuation severity (Bonanni et al., 2010). From a clinical perspective, the presence of an inverted P300 amplitude gradient differentiated DLB patients from AD patients with a sensitivity of 70 % and specificity of 97 % (Bonanni et al., 2010).

It is feasible that impaired performance in overt attentional tasks could be due to deficits in automatic pre-attentional mechanisms in LBD patients (Brønnick et al, 2010). The concept of sensory gating relates to the automatic, pre-attentional filtering of irrelevant sensory stimuli (Wan et al, 2008). Sensory gating can be assessed using the prepulse inhibition paradigm (PPI), often referred to as the P50 suppression paradigm, which involves the presentation of two auditory pulses within 50 ms of each other. In healthy individuals the second pulse is perceived as irrelevant and filtered out, this is evident as ERP waveform suppression (Oranje et al., 2006). Perriol et al. (2005) used a PPI paradigm, in which an 80 decibel (dB) auditory pulse preceded a 115dB pulse, to investigate early attentional selectivity in DLB, PDD, AD patients and controls. The percent PPI of the N100/P200 component amplitude was significantly reduced in the DLB patients compared to the AD and control groups, whilst the PDD patients exhibited intermediate PPI disturbances, whereby the percentage of PPI was significantly reduced relative to the control group. The authors suggested that the attenuated PPI in the DLB patients, indicative of a reduction in early attentional selectivity, may be due to greater dysfunction of the dopaminergic subcortico-thalamo-cortical system in DLB relative to PDD patients (Perriol et al., 2005).

To summarise, from the EEG literature, it is apparent that LBD patients exhibit aberrant oscillatory activity at rest, in particular slowing of activity and increased frequency variability, which has (to an extent) been found to correlate with the severity of clinically assessed cognitive fluctuations. Furthermore, there is some evidence to suggest that these atypical electrophysiological features of LBD are associated with reduced integrity of the cholinergic system. The limited ERP studies of LBD cohorts have demonstrated that various

ERP parameters show atypicality in DLB patients, and can be associated with cognitive fluctuation severity and reduced attentional selectivity.

Whilst these studies clearly demonstrate associations between the atypical electrophysiology and cognitive fluctuations, and pertain to deficits in attentional function, the precise aetiological mechanisms underlying the attentional dysfunction of LBD are yet to be elucidated. Further exploration of the neurophysiology underlying the attentional dysfunction, and how this relates to clinically assessed cognitive fluctuations, is essential in order to develop rational management strategies for this important clinical feature.

The Attention Network Test (ANT), discussed briefly in section 1.2.2, is an ideal task to investigate the aetiology of attentional dysfunction in LBD as it fractionates attention into three distinct components, and thus can be used to determine the specific aspects of attention which are differentially affected in LBD relative to other dementias such as AD. Furthermore, the use of the ANT in conjunction with electrophysiological recordings has potential to provide an insight into the neurophysiological basis of the fractionated facets of attention affected in LBD. The following section outlines the existing ANT literature regarding the neurophysiology of the attentional networks, and attentional network functioning in dementia cohorts.

1.5 Attention Network Test

1.5.1 Task design

The ANT, devised by Fan et al. (2002), is a computerised reaction time task designed to probe the efficiency of the three attentional networks (as discussed in section 1.2.2: alerting, orienting, and executive conflict). Figure 1.4. depicts the design of the task. An early version of the ANT was presented in a paper by Fan et al. (2002), however the task depicted in Figure 1.4 is a later version from Fan and colleagues (2007), in which the timings of the stimuli presentation were modified (compared to the previous version of the ANT) in order to optimise the task for use with fMRI and EEG recordings.

As shown in Figure 1.4, for each trial of the task there are three possible cue conditions: no cue, neutral cue, and spatial cue. In the cue-present conditions, asterisks are displayed (details of each cue condition are given in Figure 1.4.). In the no cue condition, the absence of a cueing stimulus means that the participant's attention remains diffuse across the

potential target locations. The neutral cue serves to alert the individual to the onset of the subsequent target (it is temporally informative), however the spatial cue is both temporally and spatially informative as it indicates the location of the subsequent target. Following a variable duration, one of two possible target conditions, congruent or incongruent, are presented. In the congruent target condition, a central arrow is presented with flanker arrows on each side pointing in the same direction as the central arrow, whereas in the incongruent target condition the flankers point in the opposite direction to the central arrow (for details of target stimuli see Figure 1.4.). The task is to indicate the direction of the central arrow, and responses are usually collected by pressing relevant keys on a keyboard. The ANT is conducted by presenting blocks of trials, although the number of blocks, and number of trials in each block, often vary according to the specific study.

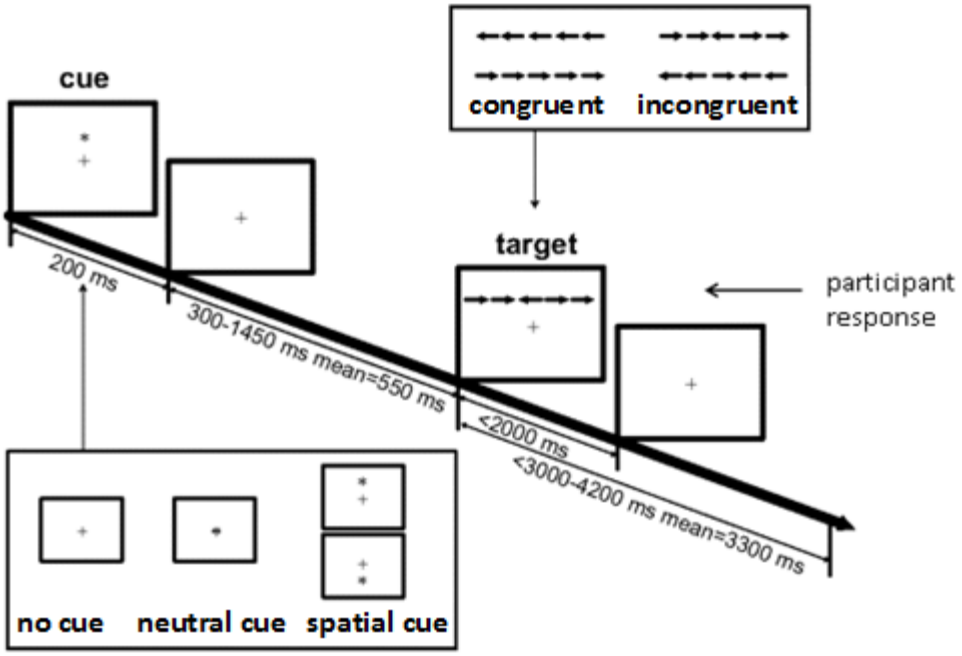


Figure 1.4. Schematic of the ANT, adapted from Fan et al. (2007).

The stimuli (cues and targets) are presented on a monitor. A central fixation cross is present on the screen throughout the task. At the start of each trial, one of a possible three cues (no cue, neutral cue, spatial cue) is presented for 200 ms. In the cue present conditions, an asterisk is displayed for 200 ms. During the neutral cue condition the asterisk is presented over the central fixation cross. In the spatial cue condition, the asterisk is either presented above or below the central fixation cross to cue the participant to the position of the subsequent target, which is presented after a variable duration (300-1450 ms). The target (the central arrow) and flankers (two arrows to the left of the central arrow, and two arrows to the right of the central arrow) are presented above or below the central fixation cross. In the congruent target condition the flankers point in the same direction as the central arrow, whereas in the incongruent target condition the flankers point in the opposite direction to the central arrow. The targets remain on screen until the participant responds (by indicating the direction of the central arrow) or until 2000 ms has elapsed. The disappearance of the target is followed by a variable inter-trial duration of 3000-4200 ms.

The cue conditions are used to measure the alerting and orienting network efficiency, whilst the target conditions (summed across all cueing conditions) are used to assess the executive conflict network efficiency. Using the behavioural (reaction time (RT)) data from the task, the attentional network effects are calculated using following network calculations devised by Fan et al. (2002):

Alerting effect = no cue $_{\text{trials mean RT}}$ - neutral cue $_{\text{trials mean RT}}$

Orienting effect = neutral cue $_{\text{trials mean RT}}$ - spatial cue $_{\text{trials mean RT}}$

Executive conflict effect = incongruent target $_{\text{trials mean RT}}$ - congruent target $_{\text{trials mean RT}}$

For studies in which participants complete the ANT whilst simultaneously undergoing neuroimaging or electrophysiological recordings, when analysing the data from these recordings it is convention to reverse the alerting and orienting network contrasts (i.e. alerting = neutral cue - no cue, orienting = spatial cue - neutral cue) in order to visualise the network effects.

1.5.2 Oscillatory activity associated with the attentional networks

A number of studies have used the ANT in conjunction with simultaneous EEG recordings to deduce electrophysiological correlates of the attentional networks. Such studies are important for understanding the temporal processes underlying the three fractionated aspects of attention. In the following paragraphs electrophysiological studies of the ANT conducted using cohorts of healthy individuals are discussed.

ERP studies

Neuhaus et al. (2010) conducted an ERP study of the ANT using a cohort of 44 healthy individuals (mean age: 30.39 years, SD: 7.1). An increase in the amplitude of the post-target N100 ERP component (evident approximately 180 ms post-stimulus) over posterior regions was found be associated with the alerting and orienting effects (i.e. alerting effect N100 was calculated by contrasting the amplitude of the target N100 following neutral cue conditions with the target N100 component following no cue conditions). In particular,

the alerting effect was associated with increased N100 amplitude over the parietal cortex, which fits with existing literature showing the parietal cortex to be a key region associated with the alerting network (Fan et al., 2005). The orienting effect was associated with increased N100 over the occipital cortex. Although orienting is typically associated with temperoparietal regions (Fan et al., 2005), the authors suggested that the enhanced occipital N100 amplitude reflects the key role of the extrastriate cortex in the generation of attention-related N100. The authors concluded that the increased amplitude of the posterior N100 is indicative of the alerting and orienting networks engaging selective attentional mechanisms during the early stages of visual processing.

Neuhaus et al. (2010) found the executive conflict effect (calculated by contrasting the activity following congruent and incongruent target trials) to be associated with increased P300 amplitude over frontal regions, and decreased P300 amplitude over parietal regions. Given that frontal P300 has been found to be associated with activity of the anterior cingulate cortex (Schmajuk et al., 2006), a key region of the executive conflict network (Fan et al., 2005), the authors suggested that the conflict effect evokes a frontal P300 component via activation of the anterior cingulate cortex. The decrease in parietal P300 amplitude may also reflect the difficulty associated with target detection (resolution of conflict), as posterior P300 amplitude has been shown to decrease with increasing task difficulty (Polich, 2007).

Fan et al. (2007) also conducted an EEG study of the ANT, with a participant cohort comprising 36 young healthy controls (mean age: 27.2 years, SD: 5.2). The main focus of this paper was to characterise the activity of the attentional networks from a frequency perspective (discussed in subsequent paragraphs); however images of ERPs associated with the cue and target stimuli were provided in the paper. Dipole modelling was used for the analyses (dipole sources were derived from clusters of activation in an fMRI ANT study). The authors did not report quantitative ERP analysis results, therefore it is difficult to make inferences with respect to ERPs associated with each of the attentional networks. From the alerting effect ERP images (calculated using the post-cue activity), there appeared to be an N100 component evident for some of the sources, in particular the left superior parietal region. ERP images for the cue conditions used to calculate the orienting effect (neutral and spatial cues) also appeared to show an N100 component for the left parietal source, as well as the right fusiform gyrus, however the waveforms appeared to be very similar for both the neutral and spatial cues. With regard to the post-target activity (used to derive the executive conflict effect), the authors noted that there were small, non-significant, differences between the congruent and

incongruent targets with regard to the N100 and P300 components, but did not explicitly state what the differences were. From the ERP images, congruent and incongruent N100 and P300 components appeared to be evident across several dipole sources, with N100 most evident for the left superior frontal gyrus, and the fusiform gyrus sources.

In an ANT EEG study of 25 healthy adults (mean age: 29.6, SD: 8.7 years), Galvao-Carmona et al. (2014) observed a post-target P100 component, which had maximum amplitude over the parieto-occipital region. The amplitude of this P100 component was found to be modulated according to the cue condition prior to the target presentation; increased amplitude was evident following the spatial cue relative to the no cue and neutral cue conditions. The authors suggested that this is indicative of enhanced processing of stimuli which are presented in the attended location. Target presentation was also found to elicit the N100 component, which also had maximum amplitude over the parieto-occipital region. The latency of the target N100 component (both congruent and incongruent conditions combined) was faster for targets preceded by a spatial cue relative to the no cue condition, indicative of spatial information regarding the upcoming target speeding early visual processing of the target stimulus. In terms of amplitude, it was found that the neutral cue increased the target N100 amplitude relative to the spatial and no cue conditions, and the authors suggested this may be explicable in terms of the need for reorientation of attention to the target when a neutral cue is presented. Due to the lack of N100 amplitude increase following a spatial cue, and the lack of amplitude difference between the no cue and spatial cue conditions, the authors speculated that the benefit of spatially orientated attention did not occur, possibly due to the cue-target interval being too long. A target P300 was also identified, which had maximum amplitude over the parietal regions. This P300 amplitude was increased following congruent targets relative to incongruent targets, which fits with the Neuhaus et al. (2010) findings, and (as previously discussed) may be due to task difficulty.

In summary, the findings of the ANT ERP studies are somewhat heterogeneous, even in healthy individuals, which may be driven by subtle differences in the ANT design used in the studies (e.g. varying cue-target intervals). However, there is some evidence to suggest the cue and target stimuli evoke comparable components, particularly N100 and P300, although the precise ERP modulations associated with the attentional networks are yet to be elucidated.

Time-frequency studies

Time-frequency analyses involve decomposition of event-related oscillations into phase and magnitude information for each frequency (or specified frequency band) at each time point, enabling spectral decomposition over time (with respect to stimulus onset) to be analysed (Roach & Mathalon, 2008). Oscillatory reactivity (event-related synchronisation and desynchronisation) derived from time-frequency analyses is a measure of task-related synchronisation of neuronal populations. Whilst ERP analyses provide information regarding the temporal processes associated with the attentional networks, time-frequency analyses approaches enable oscillatory activity to be studied in both the time and frequency domains simultaneously, and thus have potential to provide greater insight into the neurophysiological mechanisms underlying the attentional networks.

Fan et al. (2007), in an ANT study of 36 healthy participants (the ERP findings of this study are discussed in earlier paragraphs), conducted time-frequency analyses to investigate the oscillatory activity (between 4-100 Hz) associated with each of the attentional networks. The alerting network was associated with desynchronisation of theta, alpha, and beta activity between 200-450ms post-stimulus. This desynchronisation was evident across the majority of sources of interest (derived from dipole source localisation), and Fan et al. suggested that this widespread desynchronisation may indicate involvement of the thalamocortical system in regulating the alerting network. The orienting network was associated with gamma activity synchronisation at approximately 200 ms post-stimulus; this was predominantly evident in the fusiform gyrus and right superior parietal lobe sources, which implies that gamma synchronisation in these sources may have an integral role in orienting of attention. For the executive conflict effect, in the initial 400 ms post-stimulus there was event-related synchronisation over a broad range of frequencies including the gamma band; this fits with the oscillatory activity associated with the anterior cingulate cortex, which is an integral structure of the executive conflict network (Fan et al., 2005).

Deiber et al. (2013) conducted an EEG study of the ANT in order to investigate age related modulations in oscillatory activity (between 4-30 Hz); the cohort comprised 20 young and 28 healthy elderly individuals. Comparable to the Fan et al. (2007) study, there was an initial desynchronisation in the alpha and beta ranges following the presentation of both the cue and target stimuli, however, in addition, Deiber et al. observed an early synchronisation in the theta range. In the no cue condition, posterior alpha desynchronisation (prior to target onset) was diminished in the elderly group relative to the young group. Given that alpha

desynchronisation in posterior regions has been found to be associated with anticipatory attention for impending stimuli (Pfurtscheller & Lopes da Silva, 1999), the authors concluded that the elderly individuals engaged less anticipatory attentional resources than the younger individuals. Relative to the young group, the elderly group also showed attenuated mid-parietal alpha desynchronisation associated with the alerting effect, and diminished posterior alpha activation associated with the orienting and executive conflict effects. Deiber et al. (2013) concluded that there was an overall reduction in task-related alpha reactivity in the elderly individuals.

Delineating the oscillatory activity associated with the attentional networks in healthy individuals has potential implications for understanding the pathophysiology of attentional dysfunction in clinical populations. To date, the oscillatory reactivity of the attentional networks is yet to be studied in dementia cohorts such as LBD, however attentional network efficiency in dementia patients has been investigated from a behavioural perspective; this is discussed in the following section.

1.5.3 Attentional networks in dementia

The simplicity and ease of implementation of the ANT renders it an ideal task to investigate attentional function in dementia populations. Only two studies (Fernandez-Duque et al, 2006; Fuentes et al, 2010), to date, have investigated the efficiency of the attentional networks from a behavioural (reaction time) perspective in dementia cohorts.

Fernandez-Duque and Black (2006) investigated the attentional networks in a cohort 13 AD patients, and 26 healthy controls (13 young, 13 elderly). A modified version of the original ANT was used, the main modification being the use of flashing boxes as opposed to asterisks (specific details of the modified task used are discussed in chapter 3). It was found that the alerting effect increased with age, but was not significantly affected in the AD patients. There were no group effects for the orienting effect. With regard to the executive conflict effect, there was no age effect, but the efficiency of this attentional network was found to be impaired in the AD group. This fits with the extensive literature documenting executive functioning deficits in AD (McGuinness et al., 2010).

Fuentes et al. (2010) conducted an attentional network study of 13 DLB patients, 18 AD patients, and 18 age-matched healthy controls. This study used a version of the ANT which was substantially modified relative to the task; alerting was assessed using an auditory

tone (as opposed to a visual cue) which was presented prior to a visual orienting cue (which was either a valid or invalid indicator as to the location of the subsequent target). Further details of the task design are given in chapter 3. The behavioural analyses focused on the interaction between the 'alerting' cue and the executive and orienting effects. In the healthy control group, the alerting cue increased the executive conflict effect and enhanced the orienting effect. The most notable group differences were evident in the interactions between the alerting cue and the orienting and executive conflict networks; the alerting cue had a greater role in regulating the orienting and executive networks in the DLB patients relative to the AD patients.

It is evident that the literature pertaining to attentional network efficiency in dementia populations is very limited. The two studies discussed differ with regard to the participant cohorts, analyses conducted, and the versions of the ANT used; in particular, the cuing stimuli differ substantially between the two studies. From this limited literature it is therefore difficult to deduce the extent to which attentional network efficiency, as defined in the context of the original ANT, is affected in dementia populations, particularly LBD patients. To date, there is no literature pertaining to the electrophysiology of the attentional networks in dementia. Research of this nature of crucial in order to clarify the attentional networks affected in LBD, and to delineate the pathophysiology underlying the aberrant attentional functioning associated with the condition.

1.6 Aims and hypotheses

1.6.1 Study objective

The objective of this project was to use the ANT in conjunction with high density EEG recordings in order to investigate the neurophysiological mechanisms underlying the attentional dysfunction associated with LBD. Participants were recruited as part of the broader CATFieLD study (see chapter 2), and comprised 28 DLB, 25 PDD, 35 AD patients, and 22 age-matched healthy controls. Participants were assessed using a modified version of the ANT, which was adapted in order to optimise the task for use with dementia cohorts (see chapter 2, section 2.5), whilst simultaneously undergoing EEG recordings.

Attentional network efficiency in LBD was examined from two perspectives: behaviourally (chapter 3) and electrophysiologically (chapters 4-8). Given that a slowing of

oscillatory activity in LBD has been found to correlate with cognitive fluctuation severity (section 1.3.2), time-frequency analyses were conducted to investigate attentional network activity from a frequency perspective (chapters 5-8), and associations with clinically assessed cognitive fluctuations were investigated.

1.6.2 Hypotheses

- Behaviourally, given the existing literature on attentional network efficiency in dementia cohorts, it was hypothesised that the AD patients would exhibit reduced efficiency of the executive conflict network relative to the age-matched healthy controls. Given that deficits in executive functioning are a common feature of LBD, it was further hypothesised that the LBD group would also exhibit reduced executive conflict processing efficiency relative to the healthy controls. As the orienting network is modulated by the basal forebrain cholinergic system, which is markedly affected in LBD, it was postulated that the LBD patients would also exhibit reduced orienting efficiency relative to healthy controls.
- From an EEG perspective, it was hypothesised that atypical neuronal synchrony, generated by the thalamocortical system, is a contributory factor underlying the attentional dysfunction exhibited by individuals with LBD. It was therefore predicted that the LBD group would show aberrant oscillatory reactivity following ANT stimuli presentation.
- It was hypothesised that atypical oscillatory reactivity is a contributory factor underlying cognitive fluctuations in LBD. As cognitive fluctuations are postulated to be associated with cholinergic system and thalamocortical integrity, it was predicted that oscillatory reactivity associated with the orienting network in LBD would correlate with clinically assessed cognitive fluctuations. In addition, given that alerting is the ability maintain an alert state, it was hypothesised that the oscillatory reactivity associated with this network would correlate with cognitive fluctuation severity. In particular, as cognitive fluctuation severity in LBD has been found to be associated with slowing of posterior oscillatory activity, it was predicted that for these attentional networks low frequency reactivity over posterior regions would correlate with fluctuation severity

Chapter 2 . Study methodology

The objective of this chapter is to provide an overview of the CATFieLD (Cognitive and AttenTional Function in Lewy body Disease) study methodology and the clinical assessments carried out in the groups tested. Detailed descriptions of analysis methodologies (behavioural and EEG) are described in subsequent chapters.

2.1 CATFieLD study

CATFieLD study participants were assessed using a modified version of the ANT (refer to section 1.5 for details of the original task) whilst undergoing high-density EEG recordings and fMRI on two separate occasions. The focus of my PhD project was the acquisition and analysis of the EEG data. Analyses of the fMRI data will not be covered in this thesis; findings from the fMRI component of the study are reported in Firbank et al. (2015).

2.1.1 Ethical considerations

Ethical approval for the CATFieLD study was obtained from the NTW (Northumberland, Tyne and Wear) NHS trust and Newcastle University ethics committee. All participants gave written informed consent prior to study participation, however when a patient lacked capacity consent was obtained from the participant's carer in accordance with the Mental Capacity Act 2005.

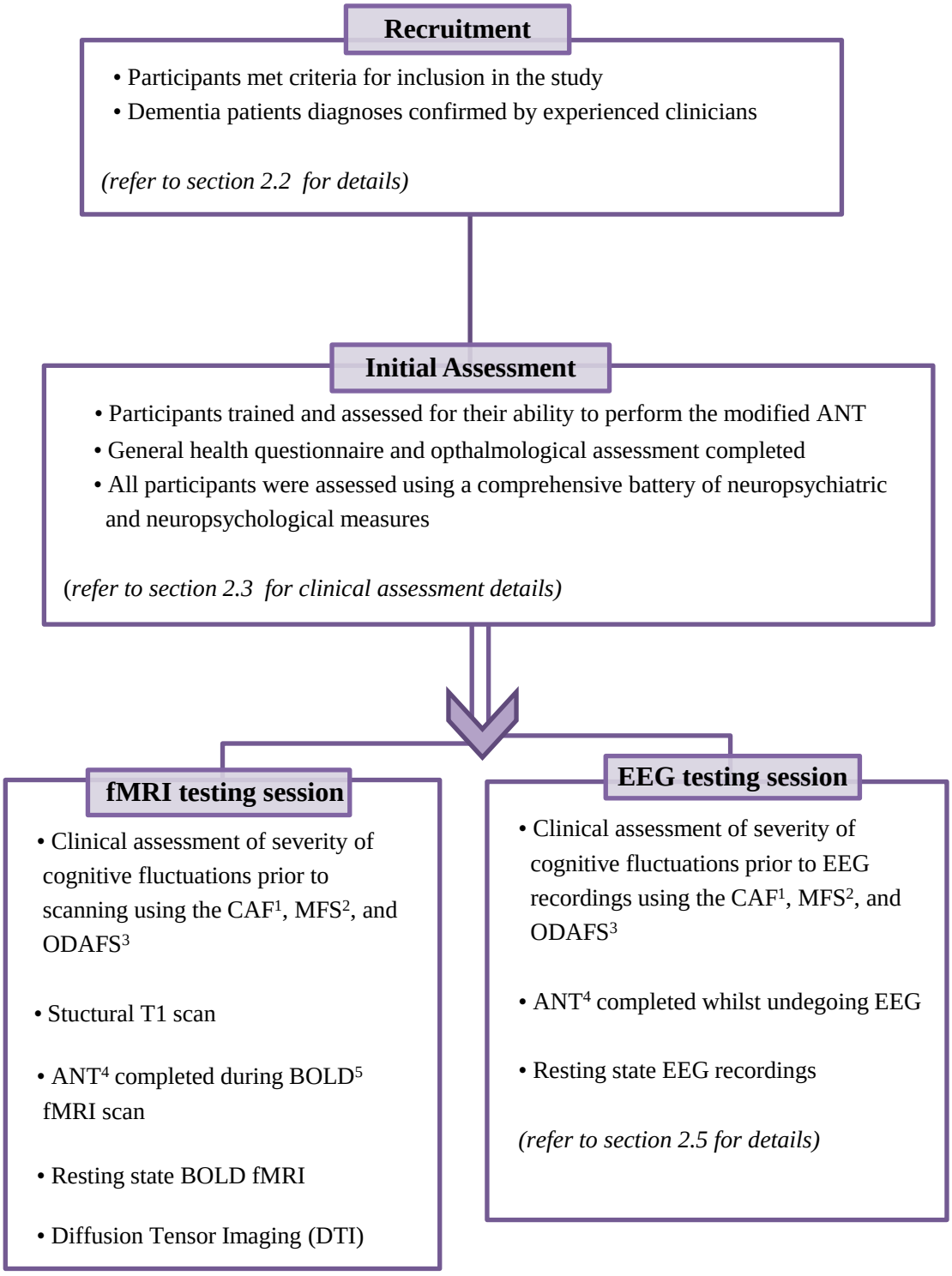
2.2 Recruitment

Individuals with dementia were recruited by North East DeNDRoN (The Dementias and Neurodegenerative Diseases Research Network) from a community dwelling population of patients who had been referred to local old age psychiatry and neurology services. Age-matched control participants were recruited from amongst relatives and friends/acquaintances of patients participating in the study, and volunteers who responded to CATFieLD study advertisements. All potential participants were screened to assess eligibility for study participation in accordance with inclusion/exclusion criteria (see section 2.2.1). Individuals

completed questionnaires regarding current health and medical history. Dementia patients additionally underwent a comprehensive physical, neurological and neuropsychiatric examination. All recruited patients met clinical criteria for dementia diagnosis; diagnoses were made by consensus agreement between two experienced clinicians. Diagnosis of probable DLB was made using the revised dementia with Lewy bodies consensus criteria (McKeith et al., 2005), and PDD patients fulfilled the diagnostic criteria for PDD (Emre et al., 2007). AD patients were diagnosed using the National Institute on Aging-Alzheimer's Association (NIA-AA) criteria for Alzheimer's disease (McKhann et al., 2011). Whilst participants lacked autopsy definitive diagnoses, clinical diagnosis of probable DLB has been found to have high specificity (95 %) with DLB neuropathology at autopsy (McKeith et al., 2000b).

2.2.1 Inclusion/exclusion participatory criteria

Given prospective difficulties regarding task comprehension amongst individuals with severe dementia, patients were required to score above 12 on the MMSE (Mini Mental State Examination- refer to section 2.3) (Folstein et al., 1975) to take part in the study. A MMSE score of 26 or below was an exclusion criterion for healthy individuals. None of the recruited healthy participants had a history of, or currently exhibited, psychiatric or neurological brain disease. Exclusion criteria for all participants were: co-morbid severe or unstable medical illnesses, and visual impairments secondary to glaucoma, cataract or macular degeneration. An additional exclusion criterion was the presence of any contraindication for magnetic resonance imaging e.g. pacemakers, cochlear implants, metal body clips. Due to ethical constraints associated with medication cessation, patients on cholinesterase inhibitors and dopaminergic medications were permitted to participate in the study. Individuals taking benzodiazepines, antipsychotics or anticonvulsants were, however, excluded (with the exception of individuals taking Clonazepam at a dose of < 0.5g or any dosage of Quetiapine), as these agents have been found to strongly affect EEG activity (Amann et al., 2003; Centorrino et al., 2002; Michail et al., 2010).



[1]CAF = Clinical Assessment of Fluctuation Scale (Walker et al., 2000b)

[2]MFS = Mayo Clinic Fluctuations Scale (MFS) (Walker et al., 2000a)

[3]ODFAS = One-Day Fluctuation Assessment Scale (Ferman et al., 2004)

[4]ANT =Attention Network Test (Fan et al., 2002)

[5]BOLD = Blood-oxygen-level dependent

Figure 2.1. CATFieLD study flowchart

Each participant recruited into the study completed an EEG and fMRI testing session on two separate occasions; the order in which the two testing sessions were completed alternated between participants. Note: as this project focuses on the EEG component of the study, the fMRI component is not discussed further in this chapter.

2.3 Neuropsychological and neuropsychiatric clinical assessments

All participants underwent an initial clinical assessment (Figure 2.1), conducted by research psychologist Ms Alison Killen in the participant's home, during which they were assessed using a comprehensive battery of neuropsychiatric and neuropsychological measures. This initial assessment was conducted in the four weeks prior to the participant completing the EEG/fMRI testing sessions. During this screening session participants completed a practice run of the modified ANT (task described in section 2.5) to test their ability to complete the task. If a participant was unable to do the task they were excluded from the study at this point. Details of the clinical measures used to assess the participants are given below:

2.3.1 Global cognitive function assessments

The following assessments were used to gauge the participants' level of global (and domain-specific) cognitive functioning.

Mini Mental State Examination (MMSE) (Folstein et al., 1975)

The MMSE is designed to assess several facets of cognitive functioning including short term memory, registration (immediate memory), language functioning, and orientation. It is a well-established tool for assessing cognitive decline in dementia cohorts. A total score of ≥ 24 (out of 30) is usually considered to be the cut-off point for normal cognitive function; lower scores are indicative of diminished cognitive functioning, and are used in conjunction with functional impairments in activities of daily living to support a diagnosis of dementia. The MMSE was used to assess the participants as it is widely considered to be a good screening tool for dementia, however it is not particularly sensitive to executive dysfunction which is common in DLB (Hoops et al., 2009).

Cambridge Cognitive Examination (CAMCOG) (Roth et al., 1986)

The CAMCOG is designed to assess numerous cognitive domains including, language abilities (comprehension, expression), memory (remote and recent), attention, praxis, calculation, abstract thinking, and perception. A total score out of 105 is calculated;

individuals with dementia usually score below 80. A cut off value of 80 has been recommended for dementia as it has been found to have a sensitivity of 92 % and specificity of 96 % in identifying patients with dementia (Roth et al., 1986).

2.3.2 Neuropsychiatric assessments

Neuropsychiatric Inventory (NPI) (Cummings et al., 1994)

The NPI is a carer-administrated questionnaire which is routinely used to assess behavioural symptoms exhibited by dementia patients. Ten behavioural domains are assessed: hallucinations, delusions, agitation/aggression, depression, anxiety, euphoria, apathy, disinhibition, irritability, and aberrant motor behaviour. A score is calculated for each aspect of behaviour based on the presence, frequency and severity of symptoms over the month prior to assessment. Higher scores are indicative of greater neuropsychiatric impairment. A limitation of the NPI when assessing individuals with DLB is that it does not include a cognitive fluctuations assessment scale, although some recent dementia studies have incorporated fluctuation scales into the NPI (Mori et al., 2012).

Cornell Scale for Depression in Dementia (Alexopoulos et al., 1988)

The scale is completed by a clinician during an interview with the carer regarding symptoms exhibited by the patient during the week prior to the assessment. The questions relate to a number of symptoms including: behavioural disturbance, physical symptoms, mood, cyclic functions and ideational disturbance. Each symptoms is rated using a scale (0-2); 0 signifies an absence of symptoms, 2 indicates severe symptoms. A total score of 12 or above is indicative of probable depression. This assessment was conducted in order to ensure that the recruited individuals were not exhibiting significant depression, as this has been found to affect reaction times and EEG activity (Chase et al., 2010; Iznak et al., 2011).

2.3.3 Neuropsychological assessments

Trail Making Test (A and B) (Reitan, 1958)

This is a pen and paper test comprising two parts; Trail A tests visuomotor control, Trail B assesses mental set shifting. Trail A is a sheet of paper on which there are 25

randomly arranged circles (numbered 1-25), participants are instructed to draw a continuous line between the circles in ascending numerical order. Trail B also comprises 25 circles, half of which contain a number (1-13), half contain a letter (A-L). The task is to connect the letters and numbers in ascending order (i.e. A to 1, B to 2.). Completion time is recorded for each Trail. Trail shift time, the difference between Trail A and B completion times, is calculated and this has been suggested to be a measure of executive functioning (Arbuthnott & Frank, 2000). Performance on the Trail Making Test (particularly Trail A) has been found to differentiate individuals with DLB and AD, with DLB patients scoring significantly lower on Trail A relative to AD patients (Ferman et al., 2006). In addition, DLB patients have been found to have poorer performance on the Trail A task relative to PDD patients (Mondon et al., 2007).

2.3.4 Motor function assessments

Given that parkinsonism is a core diagnostic feature of DLB (McKeith, 2006), patients underwent a comprehensive clinical assessment of motor functioning (UPDRS-detailed below). The results of this assessment were considered as covariates for data analyses (detailed in subsequent chapters) in order to deduce the extent to which the results of analyses were explicable in terms of motor slowing (bradykinesia) in the patients.

Unified Parkinson's Disease Rating Scale (UPDRS) (Fahn, 1987)

The motor subsection of the UPDRS was used to assess the severity of motor impairment in patients, as these items have been found to be independent from cognitive functioning (Ballard et al., 1997). This motor subsection comprises five sections; rigidity, tremor at rest, bradykinesia, action tremor and facial expression. A total score is calculated by adding the scores for each of the five sections; a score of ≥ 8 is indicative of significant parkinsonism.

Edinburgh Handedness Inventory (Oldfield, 1971)

All participants completed this 10 item questionnaire. The questions relate to hand preference for a variety of tasks including writing, drawing and throwing. A total score (out of

100) was derived from the number of left/right hand preferences; this was used to determine the handedness of the participant (left handed, right handed, ambidextrous). Only right handed individuals were recruited as handedness has been found to affect attention related EEG activity (Bareham et al., 2015).

2.3.5 Visual assessment

During the initial assessment all participants underwent a detailed ophthalmological examination which included tests of visual acuity using Landolt rings (Hohmann & Haase, 1982) and logMAR letters (Bailey & Lovie, 1976). In addition, the overlapping figures and angles tests (detailed below) were administered to assess visual perception. These visual assessments were necessary in order to ensure that the participants would be able to adequately see the modified ANT which was presented on a screen (see section 2.5). Furthermore, measures of visual function were considered as covariates for analyses of the ANT data (discussed in subsequent chapters) to ensure any group (diagnosis) effects with respect to attentional functioning were not merely explicable in terms of disparity between groups regarding visual perception/acuity.

Visuo-perceptual tasks (Overlapping figures and angels test) (Mosimann et al., 2004).

This assessment comprises two computer tasks; an angle discrimination task and an overlapping figures task. DLB and PDD patients' performance on this task has been found to be comparable, but both DLB and PDD patients have been shown to be impaired on the overlapping figures task (impaired object form perception) relative to AD patients (Mosimann et al., 2004).

Angle discrimination task

Participants were shown five standard lines at 30 degree angles to each other (forming a semi-circle), and one comparison line. There were 10 trials in which participants were asked to identify (by verbal response) which line in the semi-circle matched the angle of the comparison line. The number of correct responses was recorded.

Overlapping figures task

In each trial, four unique images of fruit, animals, clothing or utensils were presented. Participants were instructed to choose which of the four images were included in a simultaneously presented overlapping figure. The number of correct responses was recorded.

2.3.6 Clinical assessment of cognitive fluctuations

Three validated fluctuation assessment scales were used to assess severity of cognitive fluctuations: the Clinician Assessment of Fluctuation Scale (CAF) (Walker et al., 2000b), the One-Day Fluctuation Assessment Scale (ODFAS) (Walker et al., 2000a) and the Mayo Clinic Fluctuations Scale (MFS) (Ferman et al., 2004). All patients were assessed using these scales immediately prior to the EEG testing session.

Clinical Assessment of Fluctuation Scale (CAF) (Walker et al., 2000b)

The CAF is a questionnaire designed to evaluate fluctuations in cognition and levels of confusion over a period of one month prior to the assessment. The patient's carer is asked the questions by an experienced clinician. The CAF comprises two scales; one pertaining to frequency of fluctuating cognition/consciousness (0-4 rating), the second assessing the duration of fluctuations (0-4 rating). A total score is derived by multiplying the scores from the two scales; a total of 0 denotes no fluctuations, whilst a score of 12 is indicative of severe fluctuations. Whilst the CAF provides an insight into the severity of fluctuations over a period of time, administration of the scale is highly dependent upon expert clinical skills and has been found to be fairly difficult to use due to the qualitative nature of several of the questions (Lee et al., 2012).

One-Day Fluctuation Assessment Scale (ODFAS) (Walker et al., 2000a)

An experienced clinician completes the scale during an interview with the patient's carer regarding the patient on the day prior to assessment. The scale comprises seven questions relating to falls, fluctuations (confusion), drowsiness, attention, disorganised thinking, altered level of consciousness, and communication. As with the CAF, some questions require qualitative descriptions of the fluctuations from the informant. In a cohort of

DLB patients, the ODFAS was found to detect fluctuations in only the minority (46%) of patients (Bradshaw et al., 2004), suggesting the scale is not particularly sensitive to fluctuations in DLB.

Mayo Clinic Fluctuations Scale (MFS) (Ferman et al., 2004)

The MFS is a 19 item questionnaire conducted by a clinician in which the carer answers questions relating to the patient's behaviour during the past month. The scale includes questions relating to attention, fluctuations in cognition, lethargy, daytime hypersomnolence, concentration abilities and disorganised speech. A total score out of 19 is calculated as an overall indicator of the severity of fluctuations experienced by the patient. The following aspects of the scale have been found to be reliable in differentiating AD and DLB; lethargy several times a day, 2 hours or more of sleep during the day, staring into space for long periods, and disorganised/illogical flow of ideas (Lee et al., 2012).

2.4 Participants

The number of participants at each stage of the study (focusing on the EEG component of the study) is depicted in Figure 2.2. The participant cohorts for the analyses presented in this thesis are discussed in subsequent chapters: details of the participant cohort used in the behavioural analyses are presented in chapter 3, and for the EEG analyses participant cohort details are given in chapter 5. Please note that different cohorts were used for the behavioural and EEG analyses; in the behavioural analyses (chapter 3), which were conducted whilst CATFieLD recruitment was still ongoing, an LBD group comprising DLB and PDD patients was used, whereas for the EEG analyses a subsample of this group was used comprising DLB patients only. For the purposes of the present thesis, it was decided that the EEG analyses would include the DLB patients only (as opposed to also including PDD patients to form an LBD group) due to a tendency for the PDD patients' data to contain substantially more movement artefacts than the DLB group (please see chapter 4 for further details).

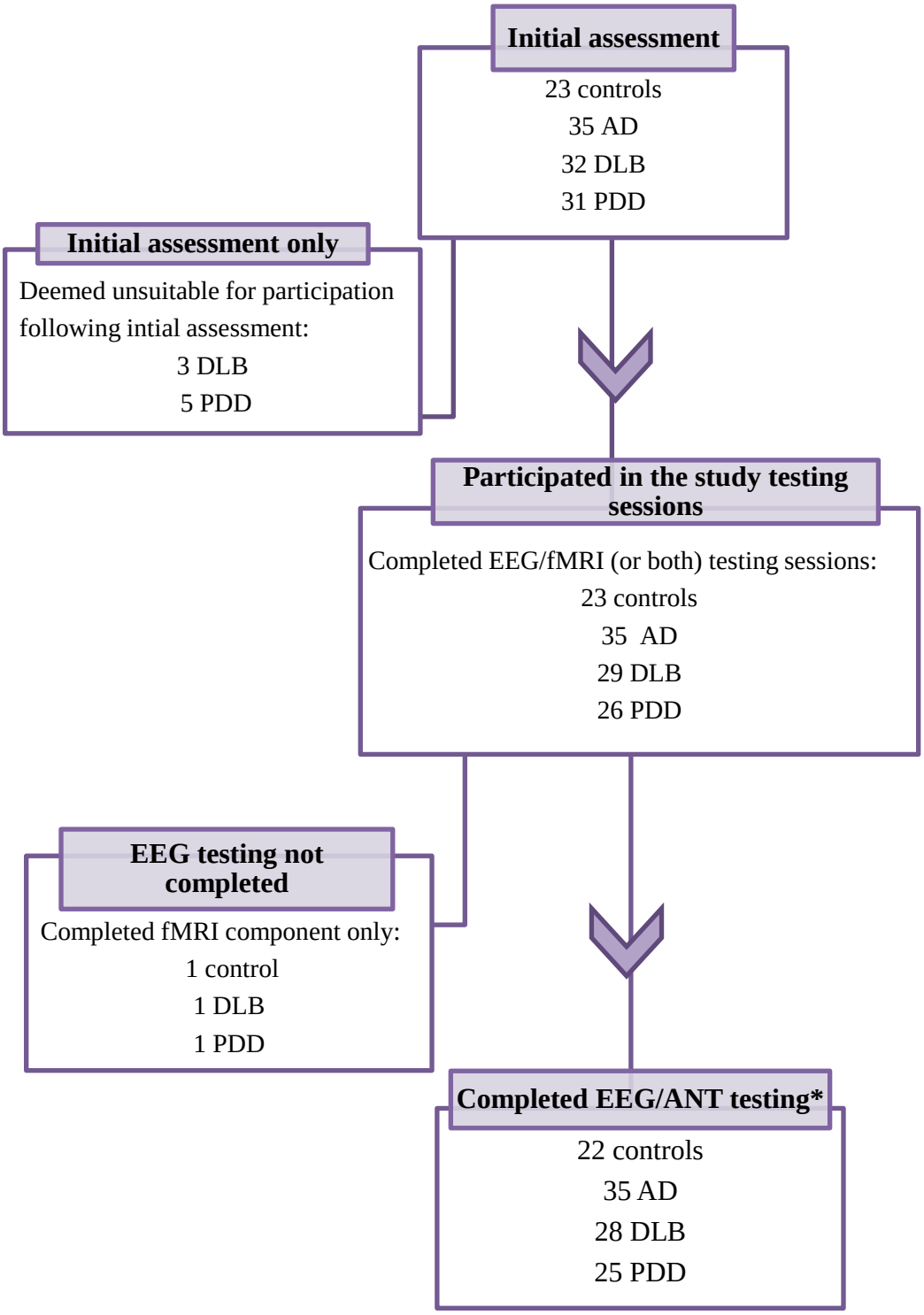


Figure 2.2. Flowchart depicting the number of participants at each stage of the CATFieLD study (focusing on the EEG component of the study). Participants who were unable to perform the task during the initial assessment were excluded. Some participants did not complete the EEG testing sessions (only the fMRI component); this was due to the participants being unable to complete the task due to fatigue, and in one case due to equipment malfunction. *Note: the number of participants listed as having completed the EEG session includes individuals whose data were later excluded due to being unsuitable for certain data analyses, due to poor task performance and noisy data (discussed in chapters 3 and 4).

2.5 Modified ANT design

The modified ANT, which is central to the CATFieLD study, probes the efficiency of the three attentional networks discussed in chapter 1; alerting, orienting and executive conflict. As with the original ANT (described in Chapter 1, section 1.5.1), to measure the alerting and orienting effects there were three cueing conditions: no cue (baseline), neutral cue (temporally informative), and spatial cue (temporally and spatially informative). The executive conflict effect was probed using congruent and incongruent target stimuli.

The rationale for modifying the original ANT design was to create a version of the task (described in section 2.5.1) suitable for probing attentional function in dementia cohorts using electrophysiological and neuroimaging approaches. As discussed in chapter 1 (section 1.5), our ANT was modelled on the version of the ANT described by Fan et al. (2007) (as opposed to an earlier version of the ANT (Fan et al., 2002)), as this version was modified to optimise the task for use with neurophysiological recordings. The timings of our modified ANT (see section 2.5.1) were largely comparable to the version of the ANT used by Fan et al. (2007); the duration of the presentation of the cueing stimuli was the same for both versions of the task (200 ms). Whilst our task incorporated an additional level of executive conflict complexity relative to the original ANT (see section 2.5.1), the majority of the design modifications were made for pragmatic purposes:

1) Given that elderly individuals tend to have reduced visual acuity relative to young adults (Sjostrand et al., 2011), and young adults were used to validate the original ANT (Fan et al., 2002), stimuli for our modified version were increased in size in comparison to the original. Furthermore, in order to optimise the task design for individuals with poor visual acuity, arrowheads were used for targets (depicted in Figure 2.3) as opposed to arrows which were used in the original task, and flashing boxes were used for the cues (see section 2.5.1) as opposed to asterisks.

2) The timings of our modified task are discussed in detail in section 2.5.1. Relative to the ANT described in the Fan et al (2007) study, the mean cue-target interval of our task (1800 ms, Figure 2.3) was longer than that of the original (mean 550 ms), and the target was presented on screen for longer (for 3000 ms as opposed to 2000 ms). These modifications were made in order to account for slower cognitive processing speed exhibited by elderly individuals relative to young adults (Hoogendam et al., 2014).

2.5.1 Task design

The computerised task was programmed by Dr Michael Firbank using the Cogent MATLAB toolbox (http://www.vislab.ucl.ac.uk/cogent_2000.php). The design of the modified ANT is depicted in Figure 2.3. There were 8 runs of the task, each comprising 36 trials. Throughout the task a central fixation cross and three boxes were present on the LCD screen. During each trial, one of three possible cues (no cue, neutral cue, spatial cue) was presented for 200 ms. During the presentation of a neutral cue the central box flashed, in the spatial cue condition one of the boxes either above or below the central fixation flashed (indicating the box in which a subsequent target would appear). In the no cue condition the boxes remained unchanged. Following the disappearance of the cue, a target comprising four arrowheads in a row (horizontal spacing of 0.48 degrees) was presented in either the box above or below the central box. The time between the disappearance of the cue and the onset of the target was one of the following exponentially distributed times: 700, 770, 850, 960, 1080, 1240, 1430, 1660, 1940, 2300, 2700, 3200 ms. The target stimuli were either congruent or incongruent; congruent targets comprised arrowheads which were all pointing in the same direction (left or right), whereas for incongruent target stimuli one arrowhead was pointing in the opposite direction to the other arrowheads. The incongruent arrowhead appeared either on the end of the row (incongruent easy) or as one of the middle two arrowheads (incongruent hard). The easy incongruent target condition had three congruent arrows in a row (unilateral flanker effect), whereas the hard incongruent condition had only two (bilateral flanker effect), and therefore provided greater conflict. The target remained on screen until the participant responded, or until 3000 ms had elapsed. The time between the onset of the target and the onset of the next trial cue was one of the following: 4300, 4500, 4750, 5000, 5350, 5700, 6100, 6400, 6800, 7200, 7700, 8300 ms, each occurred 3 times during each run (in a random order). During each run, the 9 trial types (3 cue by 3 target conditions) were presented in a predetermined counterbalanced order; each cue appeared 12 times, there were 18 congruent trials and 18 incongruent trials (equally split between incongruent easy and hard).

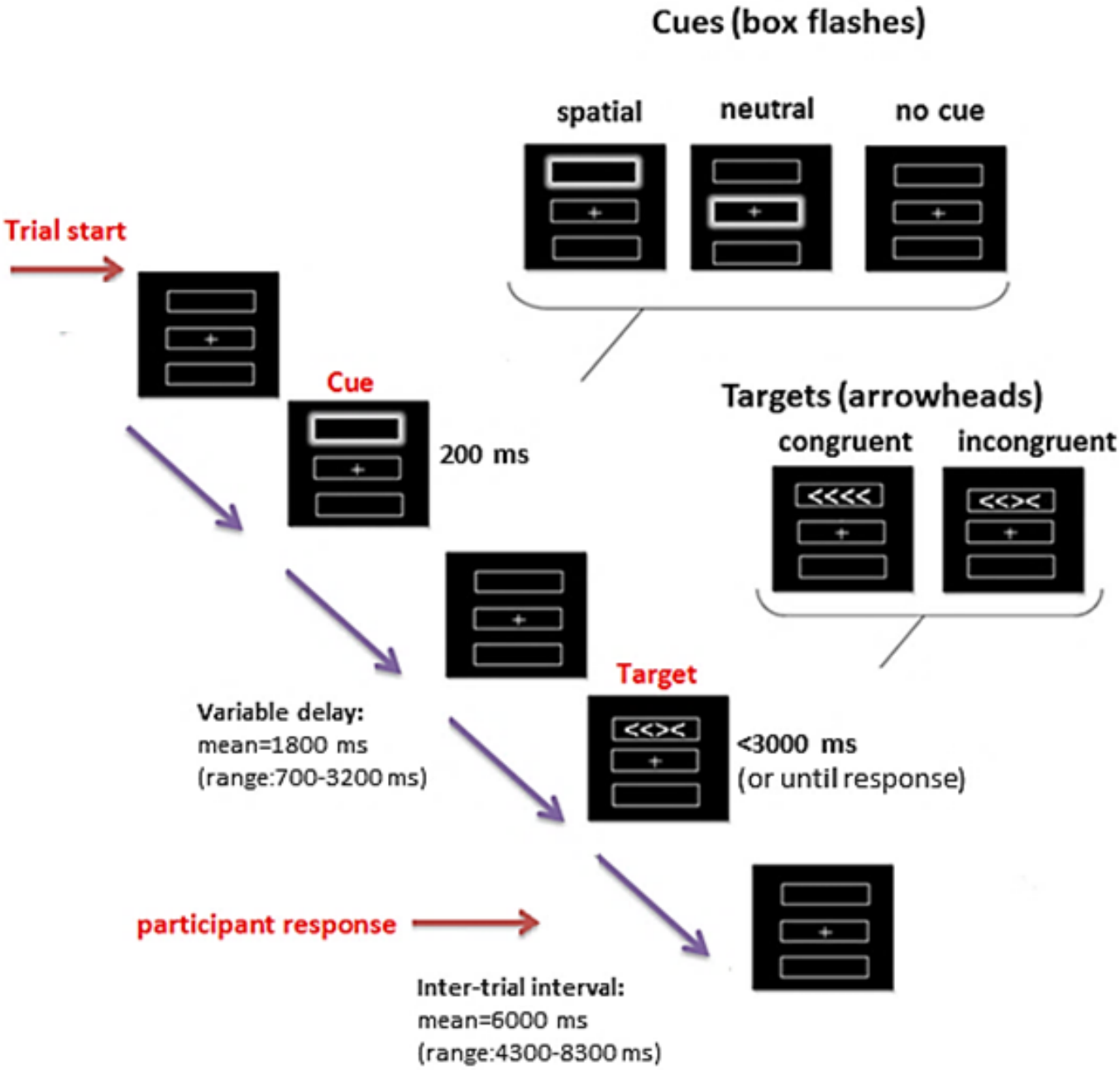


Figure 2.3. Design of the modified Attention Network Test (ANT).

Three cue conditions were presented (no cue, neutral cue, spatial cue). Two target conditions were presented (congruent and incongruent). The display consisted of a central fixation cross and three white boxes against a black background. In cue-present conditions, one of the three boxes flashed for 200 ms. During the neutral cue condition the central box flashed. During the spatial cue condition one of the boxes either above or below the central fixation flashed to cue the participant to the position of the subsequent target. Target stimuli consisted of a row of four white arrowheads pointing leftward or rightward which presented randomly in the box above or below the fixation cross. The arrowheads either all pointed in the same direction (congruent) or in opposite directions (incongruent); this defined the executive conflict component of the ANT. The objective of the task was to identify the direction in which the majority of arrowheads were facing (the points of the arrowheads) by squeezing a right hand or left hand air pressure bulb as quickly as possible.

2.6 EEG testing session

2.6.1 Protocol

I was responsible for conducting the CATFieLD EEG recording sessions. All EEG testing sessions were conducted in the Vision Laboratory, Clinical Ageing Research Unit (CARU), Newcastle University. Participants completed the modified ANT whilst simultaneously undergoing EEG recordings. Completion time for the modified ANT was approximately 40-50 minutes. All testing sessions were conducted in the morning to control for potential confounds associated with diurnal variability in attentional functioning, particularly as ANT task performance, notably the alerting benefit, has been found to vary according to time of day of testing (Knight & Mather, 2013; Matchock & Mordkoff, 2009). For all patients taking Levodopa the time since their last dose was between 1-3 hours prior to the EEG testing session; they were tested during the 'on' motor state of their medication. Cholinesterase inhibitor medication was taken as per usual.

2.6.2 EEG data acquisition

EEG data were acquired using Waveguard caps (ANT Neuro, Netherlands) comprising 128 sintered Ag/AgCl electrodes placed in accordance with the 10-5 positioning system (Figure 2.5) (Oostenveld & Praamstra, 2001). Each participant's head circumference was measured to ensure the most appropriate cap (small, medium or large) was fitted. ElectroGel (Electro-Cap International, Inc., Ohio) was syringed into each of the 128 electrode sites to bridge the conductance gap between the electrodes and the scalp. Channel signals were recorded using ASA-Lab software (ANT Neuro, Netherlands), with a sampling frequency of 1024 Hz and electrode impedances of < 5 kΩ. All electrodes were referenced to Fz and a ground electrode was attached to the clavicle. Continuous EEG data files were saved and stored for off-line data processing.

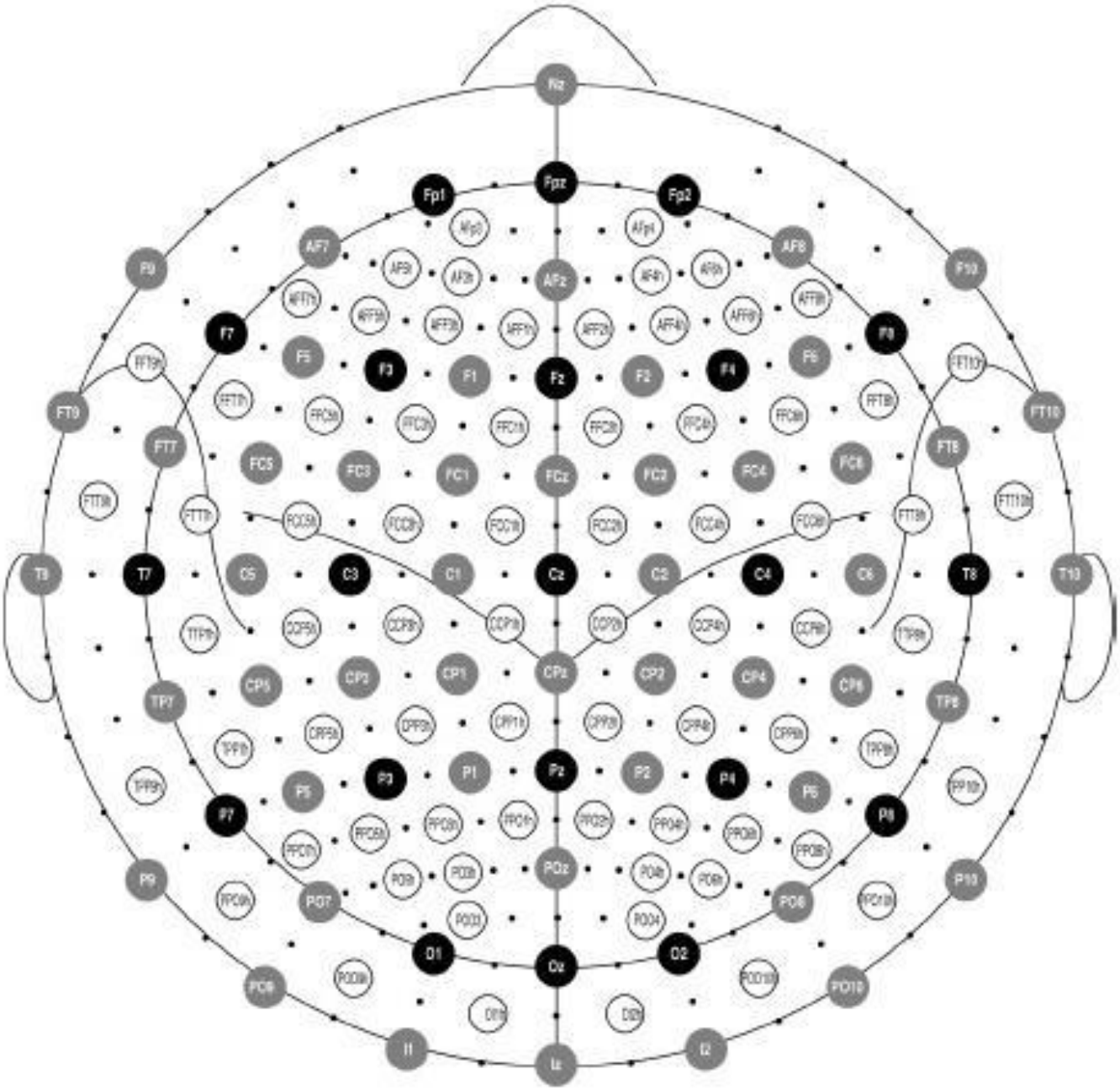


Figure 2.4. Standardised electrode positions using the 10-5 system (Oostenveld & Praamstra, 2001), a modification of the 10-20 system (Jasper, 1958) for high density EEG recordings.

2.6.3 Experimental procedure

Figure 2.5. A participant completing the modified ANT whilst simultaneously undergoing high density EEG recordings.

Modified ANT

Throughout testing participants were seated approximately 75 cm from an LCD screen (see Figure 2.6). However, the distance between the participant and the screen was adjusted (by moving participants closer/further away from the screen) to ensure that task stimuli had a spatial and size constancy in visual fields. In addition, visual refractive errors were corrected for using participants' own spectacles.

The modified ANT task was run using MATLAB 11 (The MathWorks Inc., Natick, MA, 2011). All participants received verbal task instructions; they were encouraged to maintain fixation on the central cross and were informed that they were to indicate whether the majority of arrowheads were facing left or right by squeezing the corresponding (left or right) hand air pressure bulb. Participants were asked to respond as quickly and accurately as possible. Participant responses were recorded and saved automatically as script output files. To ensure task comprehension, participants completed a practice run of the task prior to the 8 experimental runs. For motivational purposes participants received verbal feedback after each run regarding the number of correct responses and response times. Each run lasted approximately 5 minutes (dependent upon participant response times). All participants were given a short break after the first 3 runs during which they completed a short questionnaire regarding subjective task performance.

Resting state recordings

All participants underwent EEG resting state recordings. For each participant two separate recordings were conducted in succession; during eyes-open and subsequently eyes-closed conditions, each of 2 minutes 30 seconds duration. Participants were seated throughout the recordings and instructed to remain as still as possible. As these resting state recordings were conducted for the purpose of ongoing CATFieLD study research, the data from these recordings is not discussed in this thesis.

Chapter 3 . Attentional network efficiency in LBD

3.1 Introduction

The objective of this chapter is to discuss behavioural (reaction time) analyses conducted using our modified ANT. The behavioural data was considered from three perspectives:

- Validation of the modified ANT (section 3.3)
- Attentional networks in healthy ageing (section 3.4)
- Attentional networks in dementia and age-matched healthy controls (section 3.5)

In the following paragraphs, the rationale for conducting each of the behavioural analyses is discussed in conjunction with the relevant ANT behavioural literature.

Validation of the modified ANT

Prior to conducting analyses of the ANT data from our dementia patients, it was necessary to validate our modified version of the task to ensure that in healthy individuals it yielded comparable behavioural data to the original ANT. Fan et al. (2002) conducted a study using a cohort of 40 young healthy adults (mean age: 30.1 years, range: 20-44 years, 23 females, 17 males) to demonstrate that the ANT produces reliable within-subject estimates of each of the networks. Participants were tested twice on the same day, and significant test re-test reliability was observed regarding within-subject magnitude of the attentional networks (alerting, orienting, executive conflict). Although network interactions were observed, the network effects were not correlated and the authors suggested this was indicative of independence of the three attentional networks. However there was a positive correlation between the magnitude of the executive conflict effect and overall reaction time (averaged across all task conditions).

Whilst numerous studies have since validated the ANT as a reliable measure of the attentional networks, and subsequent studies by Fan and colleagues further confirmed the lack of significant correlations between the attentional network effects (Fan et al., 2007; Fan et al., 2005), there has been ongoing debate in the literature regarding the extent to which these networks are truly independent. Callejas et al. (2004) assessed 24 individuals (aged 18-23) using a modified version of the ANT (the alerting network was assessed using a high

frequency auditory cue) in order to investigate interactions between the three networks. A number of significant network interactions were observed, notably that the alerting signal lead to faster orienting. Callejas et al. (2004) postulated that although the networks are independent, the interactions amongst the networks may produce more efficient and adaptive behaviour.

Whilst the neuronal sources of the networks have been found to be anatomically distinct from one another (Raz & Buhle, 2006), behaviourally there appears to be overlap between the networks. Fan et al. (2005) suggested that a degree of interaction between the attentional networks is to be expected if the original task paradigm is substantially modified. The Callejas et al. (2004) study, as well as numerous other studies which used modified versions of the ANT, used stimuli which were presented across different sensory modalities. For example, Roberts et al. (2006) conducted an ANT study in which 40 healthy individuals completed auditory and visual versions of the ANT, and their performance on these two tasks was contrasted. Whilst the executive and alerting effects were found to be comparable across the two tasks, orienting benefits were demonstrated only for the visual task, indicative of the sensory modality of the cueing stimuli having a modulatory effect on orienting behavioural measures. The authors suggested that the executive and alerting networks were supramodal resources, whereas the disparity between the auditory and visual orienting effect may reflect modality-specific orienting perceptual processing.

As our ANT paradigm was modified relative to the original task (as discussed in chapter 2, section 2.5), the objective of the validation analysis was therefore to determine the extent to which the attentional network effects and network interactions were comparable to those reported by Fan et al. (2002). As discussed in section 3.3, a cohort of young healthy individuals, of a comparable age to the cohort assessed by Fan et al. (2002), was assessed using the modified ANT.

Attentional networks in healthy ageing

An analysis was conducted to investigate the effect of healthy ageing on attentional network efficiency and network interactions, and in particular to determine whether our modified ANT yielded comparable age related effects to the original task. Although the literature regarding attentional networks in relation to ageing is limited (Table 3.1.), a consistent trend amongst the studies is a slowing in reaction times in healthy elderly

individuals relative to healthy young cohorts. Furthermore, there is a tendency for elderly cohorts to demonstrate diminished alerting efficiency relative to young healthy individuals (Table 3.1.). Alterations in the attentional network effects with healthy ageing have been found to be evident even after adjusting for processing speed (Table 3.1, Deiber et al. (2013)), which has been found to decrease with age (Salthouse, 1996). However there is substantial variability in the findings of studies of attentional network efficiency in healthy ageing; this is likely due to heterogeneity of the studies with respect to methodologies, participant cohorts, and task design (particularly the stimuli presentation modality that is applied) (as described in Table 3.1). Consequently, from these studies it is difficult to draw valid inferences or broad conclusions regarding attentional network functioning and how it changes with age.

Attentional networks in dementia and age-matched healthy controls

A behavioural analysis was conducted in order to determine the extent to which attentional network efficiency was differentially affected in LBD patients relative to AD patients and age-matched healthy controls. As discussed in chapter 1, to date very little research has been conducted to investigate how the attentional networks are affected in dementia patients (see Table 3.2.), and the findings of these studies are inconsistent. Fernandez-Duque and Black (2006) focused on the attentional networks in AD patients relative to healthy controls, whereas Fuentes et al. (2010) investigated the attentional networks in AD and DLB patients. Furthermore, as with the studies of attentional networks in healthy ageing, the dementia studies differed with regard to the sensory modalities of the cueing stimuli; Fuentes et al. (2010), for example, assessed the alerting effect using an acoustic tone as opposed to visual cues used by Fernandez-Duque and Black (2006). From these two studies, it is therefore difficult to deduce the extent to which attentional network efficiency is affected in dementia cohorts; variability in the ANT study designs means that the findings should be interpreted in the context of the task and the specific cohort examined.

Table 3.1. ANT and healthy ageing studies

Authors (Year)	Participants	ANT	Behavioural Findings
Jennings et al. (2007)	**young adults** n=60, mean age: 19.2 years (SE: 0.12), 35 female, 25 male **healthy older adults** n=63, mean age: 69.14 years (SE: 0.83), 28 females, 35 males, mean MMSE score: 29.12 (SE: 0.12)	Original ANT (Fan et al., 2002) 20 practice trials followed by two sets of 96 trials Participants responded by pressing designated keys on the keyboard	Older adults were slower than younger adults overall. For both groups, responses were slower for incongruent compared to congruent targets. **Network effects:** The older adults showed significantly less alerting relative to the young adults. There were no differences between the groups regarding orienting or executive conflict effects (when adjusted for processing speed).
Mahoney et al. (2010)	**non-demented older adults** n=184, mean age: 80.41 (S.D: 4.68), 72 males, 112 females .	Variant of the original ANT (Fan et al, 2002) with enhanced size and luminosity of the stimuli (cue and target) The left/right mouse buttons were used to indicate the direction of the central arrow	**Network effects**: Overall significant main effects for the three attention networks, and reduced alerting but enhanced orienting effects during incongruent conflict resolution trials. Increased age was associated with reduced executive conflict processing efficiency.
Gamboz et al. (2010)	**young adults** n=70, mean age: 25.8 years (SD: 4.0) **older adults** n=65, mean age: 67.9 years (SD:5.6), MMSE $\geq$ 26	Original ANT (Fan et al., 2002) 20 practice trials followed by three sets of 96 trials	**Network effects:** Equivalent orienting and executive conflict resolution effects in the young and older adults. Alerting was significantly reduced in the older adults.

Table 3.1 (continued). ANT and healthy ageing studies

Authors (Year)	Participants	ANT	Behavioural Findings
Vazquez-Marrufo et al. (2011)	**young adults** mean age: 32.5 years (SD:9.7) **healthy elderly adults** mean age: 62.7 years (SD:4.7)	A modified version of the ANT; small boxes were used for the cues as opposed to asterisks, and the cue to target interval was fixed but increased in duration (850 ms as opposed to 400 ms) relative to the original (Fan et al., 2002).	**Network effects:** There were no differences between the young and elderly group regarding the attentional network effects.
Mahoney et al. (2012)	**young adults** n=18, mean age: 19.17 years, (SD:7.91), 45% female **non-demented elderly adults** n=18, mean age:76.44 (SD: 2.66), 61% female	Modified version of the original ANT was used to investigate the effect of multisensory cues on attention in ageing. A variety of unisensory (auditory or somatosensory) and multisensory (auditory-somatosensory (AS), auditory-visual (AV), or visual-somatosensory (VS)) alerting and orienting cues were presented prior to target presentation (target stimuli were the same as the original ANT).	**Network effects:** Both groups (young and old) demonstrated significant orienting effects for AS, AV, and VS cues. The alerting effects were not significant. The younger group demonstrated greater reaction time benefits for AS orienting cues, whereas the older group demonstrated greater reaction time benefits for AV orienting cues. Both groups demonstrated significant reaction time benefits for multisensory VS orienting cues.
Noh et al. (2012)	**young adults** n=76, 18-25 years, 44 females **elderly adults** n=69, 60-85 years, 53 females	ANT (Fan et al, 2002) 24 practice trials (with feedback following errors), followed by three experimental blocks (96 trials/block without feedback). Investigated the association between current affective state (positive/negative) and attentional network functioning in relation to age. Current affective state measured using the PANAS (Watson et al., 1988); a 20 item, self-rated measure	**Network effects:** The older group exhibited decreased alerting efficiency relative to the younger group. There was no difference between the two groups regarding the orienting and executive network functioning. **Network interactions:** Age related differences in alerting efficiency were modulated by positive affect; the older adults reported more positive affect relative to the younger adults, and this higher positive affect was associated with reduced alerting efficiency.

Table 3.1 (continued). ANT and healthy ageing studies

Authors (Year)	Participants	ANT	Behavioural Findings
Deiber et al. (2013)	**young adults** n=20, mean age: 25.5 years, (SD: 4) **elderly adults** n=28, mean age: 64.9 years, (SD:5.3)	A modified version of the ANT; the cue-target interval was fixed but of greater duration (1600 ms as opposed to 400 ms) relative to the original, and the cue was presented for longer (400 ms). Training block of 16 trials (with feedback) completed prior to 2 blocks of 96 trials. Participants completed the ANT whilst undergoing EEG recordings (to investigate age-related modulations of oscillatory activity associated with the attentional networks. The EEG findings of this study are discussed further in chapters 5 and 8).	Attentional network effects were calculated using normalised reaction times; the mean reaction time for each task condition was divided by the participant's overall reaction time (across all trials). **Network effects:** The alerting and executive conflict effects were comparable between the young and elderly groups. The orienting effect was greater in the older group relative to the younger group.

Table 3.2. ANT and dementia studies

Authors (Year)	Participants	ANT	Behavioural Findings
Fernandez-Duque and Black (2006)	**Alzheimer's disease (AD) patients** n=13, mean age: 74.7 (SD:6.7) MMSE mean: 24.3 (SD: 2.5), 7 female, 6 male. 9 of the patients on cholinergic medication **healthy controls** (n=26) *13 young*: mean age: 19.8 years (SD: 1.3), 7 female, 6 male *13 older*: mean age: 72.5 years (SD: 5.7), 7 female, 6 male	Modified version of the ANT. 2 boxes (above and below the fixation cross) remained on screen throughout the task. For the neutral cue both boxes flashed (as opposed to an asterisk appearing as in the original). The spatial cue was either valid (box in which the target would appear flashed) or invalid (target appeared in the other box). The cue-target interval was 500 ms, the target remained until a response (using keyboard keys) or 5 seconds elapsed. 5 blocks of trials (with short breaks between blocks), each block 48 trials (240 in total) + 10 trial practice block	Calculated reaction times and normalised scores (median reaction time for each task condition divided by the participant's overall reaction time). The transformed and un-transformed data were comparable. **Network effects:** Alerting effect increased with age (but not AD).There were no groups effects for the orienting effect. There was no age effect for the executive conflict effect, but conflict resolution was impaired in AD. **Network interactions:** Alerting (presence of a spatially neutral cue) increased the congruency effect.
Fuentes et al. (2010)	**Dementia with Lewy bodies (DLB) patients** n=13**,** mean age: 76 years (SD:9), 4 female, 9 male , MMSE mean: 22 (SD: 3) **Alzheimer's disease (AD) patients** n=18, mean age: 72 years (SD:9) 10 female, 8 male MMSE mean: 20 (SD:3) **healthy controls** n=18, mean age: 70 years (SD:9), 9 female, 9 male	Modified version of the ANT. Alerting was assessed using an auditory tone. This 2000 Hz tone was presented for 50 ms only in half of the trials. This was followed (after 350 ms) by an orienting cue (asterisk in box above or below fixation- either the same box as the target or the other box). Cue-target interval was either 50 ms or 450 ms. The target was present until a response (using left/right response box keys). 10 practice trials (with additional blocks of 10 trials until there were ≥ 9 correct responses). 288 trials (3 blocks of 96 trials). Rest periods every 48 trials.	The DLB group had slower reaction times relative to the AD and control groups. **Network interactions:** In controls the alerting cue increased the executive effect and enhanced the orienting effect. The most notable group differences were the network interactions; the alerting cue had a greater role in regulating the orienting and executive networks in the DLB patients compared to AD.

3.1.1 Hypotheses

As discussed in chapter 1 (section 1.6.2), given the existing literature pertaining to the attentional networks in dementia cohorts, it was hypothesised that the AD patients would exhibit reduced executive conflict efficiency relative to the age-matched healthy controls. In addition, given that deficits in executive functioning are a common feature of LBD, it was hypothesised that the LBD group would also exhibit reduced executive conflict processing efficiency relative to the age-matched controls. As the orienting network has been suggested to be modulated by the basal forebrain cholinergic system, which is markedly affected in LBD patients, it was postulated that the LBD patients would also exhibit reduced orienting efficiency relative to the controls.

3.2 Modified ANT behavioural analysis

3.2.1 Participants

For details regarding the participant recruitment and initial screening procedure please see chapter 2. The final experimental cohort comprised 63 healthy participants, 32 LBD patients and 27 AD patients. As discussed in chapter 2, for the purposes of the behavioural analyses DLB and PDD patients were grouped together; the LBD patient group comprised 18 DLB and 14 PDD patients. Preliminary analyses showed that there were no differences between the DLB and PDD patients in terms of the key behavioural effects and interactions. The dementia patients (aged 62-89 years) and 21 healthy elderly individuals (aged 62-83) were recruited from the CATFieLD study. An additional 42 healthy participants (aged 19-94) were recruited in order to validate the modified ANT in young healthy controls (section 3.3), and to aid characterisation of attentional network changes with healthy ageing (section 3.4). These additional healthy controls underwent the same recruitment and initial screening procedure as the CATFieLD study participants.

To ensure any group differences in reaction time data were not due to a lack of task comprehension amongst the dementia patients, individuals with a response rate < 60 %, and those with a response rate > 60% but < 60% of responses correct, were also excluded. The same cut-off value was used for the EEG analyses; this cut-off value ensured that there was sufficient data for both the behavioural and EEG analyses (as described in chapter 4). Using this cut off rate, 3 AD and 3 LBD potential participants were excluded from the behavioural

analyses, leaving 27 AD and 32 LBD patients. Demographic details of the participant cohorts used for each of the analyses are described in the following results sections (sections 3.3-3.5).

3.2.2 Procedure

For participants recruited from the CATFieLD study all testing sessions were conducted in the Clinical Ageing Research Unit (CARU), Institute for Ageing and Health, Newcastle University (see chapter 2). These participants completed the modified ANT whilst simultaneously undergoing EEG recordings. The additional healthy participants (not recruited as part of the CATFieLD study) were recruited by William Solyom, an undergraduate student who conducted a validation study of the modified ANT with Dr John-Paul Taylor. These participants underwent the same ANT testing procedure as the CATFieLD participants but the testing was conducted by William Solyom in the participants' homes, and without simultaneous EEG recordings.

3.2.3 Analysis method

A MATLAB script, written by Dr Michael Firbank, was used to convert the raw data from the ANT output files to reaction times and standard deviations for each cue (no cue, neutral, spatial) by target (congruent, incongruent) condition. These values were calculated for each task trial (for each participant). Using only the trials in which the participants gave correct responses, the mean reaction times (RT) (across all trials) and standard deviations were calculated for each cue and target condition. The attentional networks were calculated using the network calculations as devised by Fan et al (2002):

Alerting effect = no cue trials $_{\text{mean RT}}$ - neutral cue trials $_{\text{mean RT}}$

Orienting effect = neutral cue trials $_{\text{mean RT}}$ - spatial cue trials $_{\text{mean RT}}$

Executive conflict effect = incongruent target trials $_{\text{mean RT}}$- congruent target trials $_{\text{mean RT}}$

To calculate the alerting and orienting effects, the mean RTs were calculated by averaging the across the congruent and incongruent target trials. Similarly, the mean RTs for the target trials used to calculate the executive conflict effect were calculated by averaging across all of the cue conditions.

Error rates were also calculated for each task condition (cue and target) and each of the attentional networks (using the subtraction approach described above). Error rates were calculated for each participant by dividing the total number of incorrect and missed response trials by the total number of trials. Note error rates are not reported for the validation analyses (section 3.3) given error rates were minimal in the young healthy cohort used for these analyses, and were comparable across task conditions.

3.2.4 Statistical analysis

All of the analyses (sections 3.3-3.5) were conducted using SPSS 19.0 (SPSS Inc, Chicago), and an alpha value of 0.05. For each of the ANOVA analyses discussed below, Mauchly's sphericity test was used and F values adjusted accordingly, and post-hoc pairwise comparisons were performed using Bonferroni correction for family-wise errors.

Validation of the modified ANT (section 3.3)

For the mean RT data, repeated measures (cue x target) ANOVAs were conducted to investigate the cue and target interactions, and post-hoc pairwise comparisons were used to investigate the RT differences between the cue and target conditions; thus determining whether the attentional network effects were significant. To investigate the independence of the attentional networks, Pearson's *r* bivariate correlations were used to investigate the associations between each of the attentional network effects (alerting, orienting and executive conflict). Person's *r* correlations were also used to determine the association between each of the attentional network effects and the overall mean RT (RT averaged across all task conditions, correct responses only).

Attentional networks in healthy ageing (section 3.4)

In order to investigate how the overall mean RT changed with healthy ageing, a linear regression analysis was conducted. Linearity of the data is an assumption of this ANOVA analysis approach, however when plotting the data (see section 3.4.2) it was apparent that the best fit to the data was a quadratic relationship between overall mean RT in the healthy controls and age. However, when age was modelled as age^2 the relationship between overall mean RT and age was linear, hence age^2 (as opposed to age) was used for the healthy ageing

analyses (see section 3.4.2 for further details). For the regression analyses, the independent variable was age^2, and the dependent variable was overall mean RT (averaged across all task conditions).

To investigate the mean RT data for each task condition, repeated measures (cue x target) ANOVAs were conducted with age^2 as a covariate to determine the cue and target interactions, and post-hoc pairwise comparisons were used to calculate the attentional network effects. Comparable cue x target repeated measures ANOVAs, with age^2 as a covariate, were conducted for the error rate data. For each of the attentional networks, separate regression analyses were conducted with age^2 as the independent variable, and the network effect (alerting, orienting, or executive conflict) as the dependent variable.

To investigate the independence of the attentional networks, Pearson's *r* partial correlations were conducted using age^2 as a covariate. Partial correlations (with age^2 as a covariate) were also used to determine the association between each of the attentional network effects and overall mean RT (across all task conditions).

Attentional networks in dementia and age-matched healthy controls (section 3.5)

To determine whether the healthy controls and dementia groups differed in terms of overall mean RT, a univariate ANOVA analysis was conducted with overall mean RT as the dependent variable and group (AD, LBD, age-matched controls) as the fixed factor.

For the mean RT data for each task condition, repeated measures (cue x target) ANOVAs were conducted with a between-subject factor of group (AD, LBD, age-matched controls). For each group, post-hoc pairwise comparisons were used to calculate RT differences between the cue and target conditions, in order to determine whether each of the attentional network effects were significant. Comparable cue x target repeated measures ANOVAs, with group as a between-subject factor, were also conducted for the error rate data. Given that cholinesterase inhibitor usage has been found to enhance attentional function in dementia cohorts (Emre et al., 2004; McKeith et al., 2000a), medication usage was initially considered as a covariate in the mean RT and error rate analyses models (cholinesterase and dopaminergic medication usage were considered), but was subsequently removed due to an absence of main effects and interactions.

To investigate the independence of the attentional networks, for each group Pearson's *r* bivariate correlations were conducted to determine the association between each of the attentional network effects. For each group, correlations were also conducted between each of the attentional network effects and the overall mean RT (across all task conditions). Correlation analyses (using Pearson's *r*) were also conducted to investigate associations between the behavioural data (overall mean RT, attentional network effects and error rates) and clinical variables in the dementia groups. Clinical variables investigated included: measures of global cognitive functioning (CAMCOG and MMSE total score), clinical measures of cognitive fluctuations (CAF, MFS, ODFAS), and UPDRS motor subscale total score (details of these clinical assessments are given in chapter 2). For the purposes of clarity, for the clinical correlation analyses, only the correlations which yielded significant results are reported in this chapter. Due to the exploratory nature of these analyses, relationships are reported uncorrected for family-wise errors.

3.3 Validation of the modified ANT

3.3.1 Participants

For the modified ANT validation analyses, the participant cohort comprised 20 healthy individuals, 12 males and 8 females, under 45 years old. The mean age of the participants was 29.50 years (SD: 8.48), ranging from 17- 42 years old. The mean age of the participants was comparable to the participants in the Fan et al. (2002) study; the mean age of participants used to validate the original ANT was 30.1 years, with a range of 20 - 44 years. Our young healthy participant cohort had a mean MMSE score of 29.90 (SD: 0.45).

3.3.2 Results

Table 3.3 shows the young healthy participants' mean RT (for correct responses only) for each task condition (cue and target). There was a main effect of cue (Table 3.4), with a faster mean RT for neutral cue trials (551.68 ms, SE: 20.53) relative to no cue trials (570.01 ms, SE: 22.61), and therefore there was a significant alerting effect ($p = 0.01$) (see Table 3.5 for attentional network values). Mean RT for spatial cue trials (493.19 ms, SE: 17.52) was faster than neutral cue trials resulting in a significant orienting effect ($p < 0.001$). There was also a significant target effect, with a faster mean RT for trials in which a

congruent target was presented (458.85 ms, SE: 12.29) relative to incongruent target trials (617.74 ms, SE: 28.26), and thus a significant executive conflict effect (p <0.001).

Table 3.3. Mean RT (ms) (correct responses only) for each task condition (cue x target) for healthy controls < 45 years old. Standard deviations are presented in italics.

	controls < 45 (n=20)	
Cue	**Target**	**Mean RT (ms)**
No cue	Congruent	478.82 *(62.89)*
	Incongruent	661.21 *(144.10)*
Neutral	Congruent	472.89 *(60.11)*
	Incongruent	630.46 *(126.45)*
Spatial	Congruent	424.82 *(44.32)*
	Incongruent	561.55 *(117.00)*

Cue x target interactions were significant (Table 3.4, and depicted in Figure 3.1); overall the mean RT was greater for incongruent trials relative to congruent trials (see Table 3.3) for each type of cue: no cue (p <0.001), neutral (p <0.001) and spatial cue trials (p <0.001). There was a larger alerting effect for incongruent target trials relative to congruent trials (p<0.01); the alerting effect did not reach significance for congruent trials (p = 0.12) but was significant for incongruent trials (p <0.01). Overall the orienting effect was significant for both congruent (p <0.001) and incongruent trials (p <0.001), however this effect was larger for incongruent trials relative to congruent trials (p = 0.05). From the perspective of the executive conflict effect, this was larger for no cue trials relative to neutral cue (p <0.01) and spatial cue trials (p <0.001). The executive conflict effect was also larger for neutral cue trials than spatial cue trials (p = 0.05).

Table 3.4. The F value, p value, df, and error df for the main effects and interaction effects from the repeated measures (cue x target) ANOVA for controls < 45 years old.

ANOVA factor	Mean RT (ms)
cue	$F(1.43, 27.05) = 60.25$, $p < 0.001$
target	$F(1,19) = 79.37$, $p < 0.001$
cue x target	$F(2,38) = 12.21$, $p < 0.001$

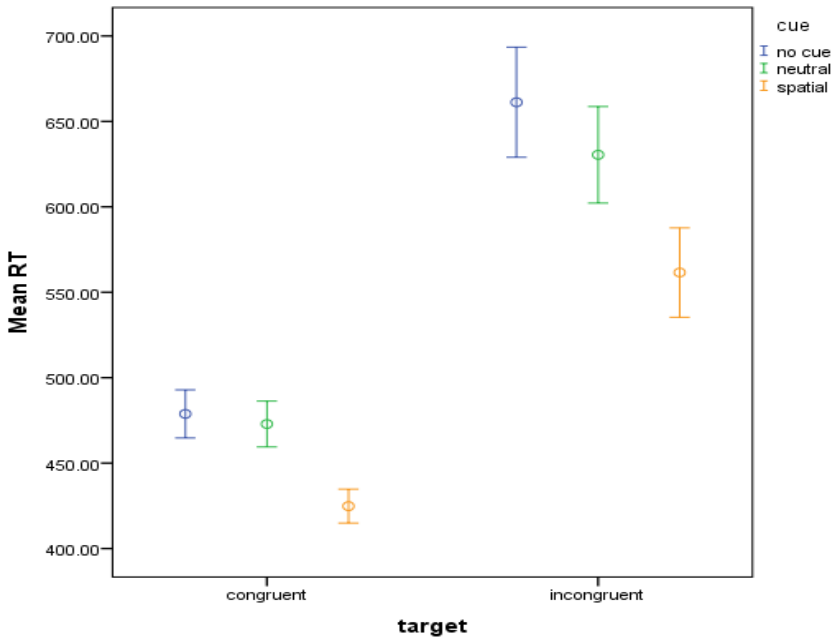


Figure 3.1. Correct mean RT (ms) for each task condition (cue x target) for healthy controls < 45 years old. Error bars represent ± 1 SE of the mean.

Table 3.5. Attentional network effects for controls < 45 years old. Network values calculated using correct mean RT are presented. Standard deviations are shown in italics.

Attentional network effect	controls < 45 (n=20)
	Mean RT (ms)
Alerting	18.33 (*22.16*)
Orienting	58.49 (*32.36*)
Executive conflict	158.90 *(76.67)*

Network independence

There were no significant correlations between any of the networks (Table 3.6). There was an association between overall correct mean RT (across all cue and target conditions) and the orienting effect, and consistent with the findings of Fan et al (2002) there was also an association between overall mean RT and the executive conflict effect.

Table 3.6. Correlation analyses between attentional networks (*p* values are shown in brackets) and overall mean RT.

	Alerting	**Orienting**	**Executive conflict**	**Correct mean RT (ms)**
controls < 45 (n= 20)				
Alerting	-	.09 (.70)	.34 (.14)	.39 (.09)
Orienting	.09 (.70)	-	.37 (.11)	.46 (.04)*
Executive conflict	.34 (.14)	.37 (.11)	-	.91 (<.001)*

*Correlation is significant at the 0.05 level (2-tailed)

3.3.3 Summary

- In the cohort of young healthy individuals assessed using our modified ANT there were significant alerting, orienting and executive conflict effects.
- The magnitude of the orienting effect was comparable to that reported by Fan et al. (2002), however the alerting effect was smaller, and the executive conflict effect larger (Fan et al. (2002): alerting: 47 *(SD:18)*, orienting: 51 *(SD:21)*, executive conflict: 84 *(SD:25)*).
- Comparable to the Fan et al. (2002) findings using the original ANT, there were no correlations between the attentional network effects. There were however positive correlations between the overall mean RT and the magnitude of the orienting and executive conflict effects.

3.4 Attentional networks in healthy ageing

3.4.1 Participants

For the analyses to investigate the effect of healthy ageing on mean RT and attentional network efficiency, the participant cohort comprised 63 healthy individuals (from the CATFieLD study and the ANT validation study). The mean age of the participants was 57.16 years (SD: 22.04), with a range of 17- 94 years.

3.4.2 Results

Overall mean RT

With increasing age there was an increase in overall mean RT (across all task conditions). This positive relationship between age and overall mean RT was non-linear (Figure 3.2 (a)). With transformation (age^2) there was a linear relationship with overall mean RT (β = 0.88, p <0.001; Figure 3.2 (b)). Therefore age was modelled as age^2 (as discussed in section 3.2.3), with age^2 accounting for 78 % of the variance in mean RT in the controls (R^2 = 0.78, F(1, 61) = 211.40, p <0.001).

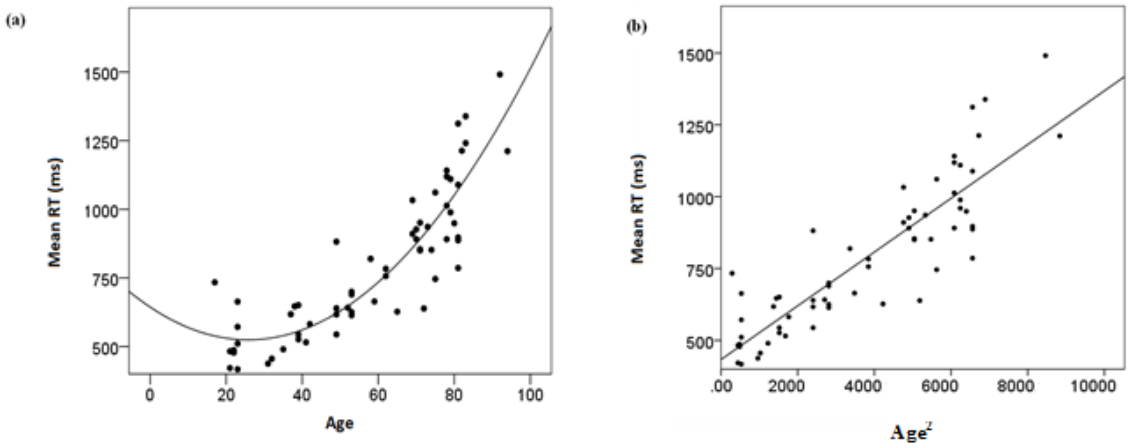


Figure 3.2. (a) Mean RT (correct responses) as a function of age (years) for all healthy controls (n=63). **(b)** Mean RT (correct responses) as a function of age^2 for controls (n=63). A linear fit well approximates the relationship between age^2 and mean RT (R^2 = 0.78)

Attentional network effects

Similar to the young adult validation cohort in section 3.3, across the age range there was a main effect of cue (Table 3.7), with a faster mean RT (p <0.001) for the neutral cue (802.61 ms, SE: 16.17) relative to no cue trials (828.42 ms, SE:16.39), and thus there was a significant alerting effect (25.81, SD: 4.63). Mean RT for spatial cue trials (727.08 ms, SE:14.39) was faster (p <0.001) than neutral cue trials mean RT, resulting in a significant orienting effect (75.53, SD: 5.76). There was also a main effect of target, with faster (p <0.001) mean RT for congruent target trials (638.35 ms, SE: 10.02) relative to incongruent trials (933.72 ms, SE: 22.64), and by extension a significant executive conflict effect (295.37, SD: 16.89).

With increasing age (modelled as age^2) there was an associated increase in RT for each cue condition; no cue (R^2 = 0.77, β = 0.88, F(1, 61) = 206.18, p <0.001), neutral cue (R^2 = 0.76, β = 28.64, F(1, 61) = 190.62, p <0.001), spatial cue (R^2 = 0.77, β = 0.88, F(1, 61) = 209.44, p <0.001). The cue x age^2 interaction (Table 3.7) was explicable in terms of the differential rates of RT increase with increasing age for each cue; the rate of RT increase with age^2 was greater for no cue trials relative to neutral and spatial trials (Figure 3.3). There was also an increase in congruent mean RT (R^2 = 0.79, β = 0.89, F(1, 61)= 228.90, p <0.001) and incongruent mean RT (R^2 = 0.73, β = 0.86, F(1, 61) = 168.44, p <0.001) with increasing age^2. The significant target x age^2 interaction was due to the greater rate of increase in mean RT with age^2 in incongruent trials relative to congruent trials (Figure 3.4).

Table 3.7. The F value, p value, df, and error df for the main effects and interaction effects in the repeated measures (cue x target) ANOVA, with age^2 as a covariate.

ANOVA factor	Mean RT (ms)
cue	F(1.77, 107.72) =18.29, p <0.001
target	F(1, 61) = 5.18, p = 0.03
cue x target	F(2, 122) = 1.02, p = 0.36
age^2	F(1, 61) = 210.22, p <0.001
cue x age^2	F(1.77, 107.72) = 11.45, p <0.001
target x age^2	F(1, 61) = 70.06, p <0.001
cue x target x age^2	F(1.77, 107.72) = 0.91, p = 0.43

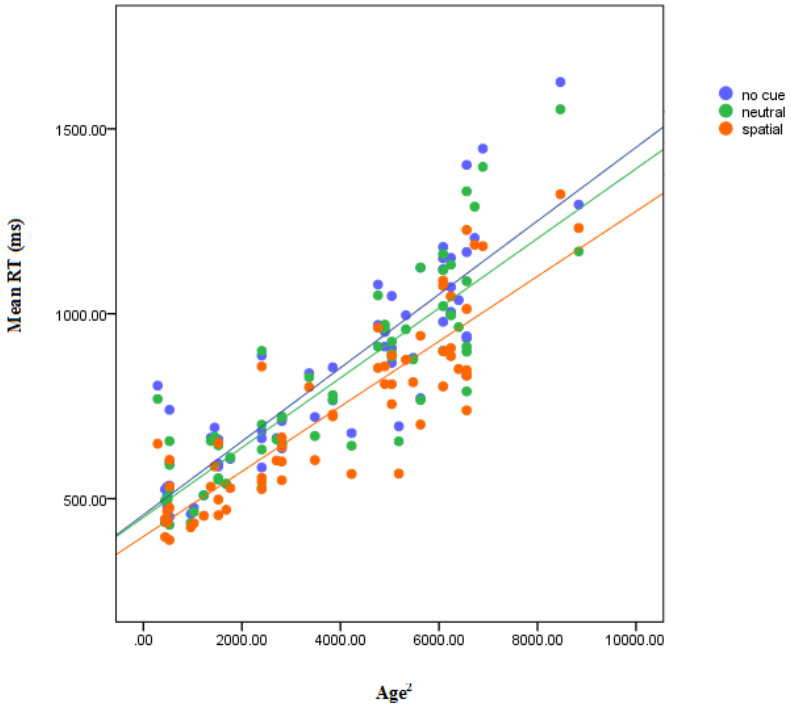


Figure 3.3. Correct mean RT (ms) for each cue condition as a function of age^2 for all controls (n=63). Regression lines: no cue (y = (0.10) x + 456.28), neutral (y = (0.09) x + 449.54), spatial (y = (0.09) x + 397.71).

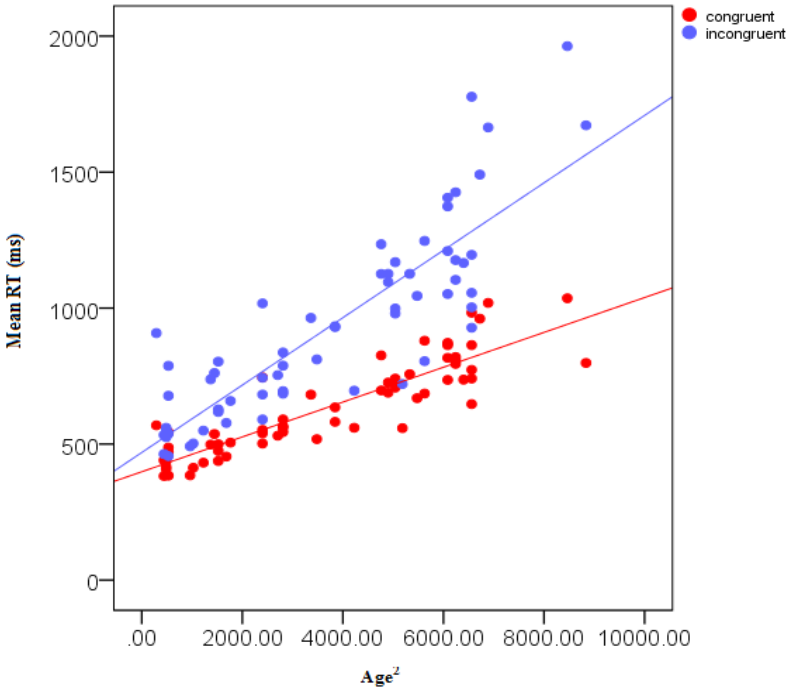


Figure 3.4. Correct mean RT (ms) for each target condition as a function of age^2 for all controls (n=63). Regression lines: congruent (y = (0.01) x + 398.47), incongruent (y = (0.12) x + 469.19).

Attentional network effects with ageing

There was an increase in the magnitude of each of the attentional network effects with increasing age^2 ; alerting (R^2 = 0.10, β = 0.32, F(1,61) = 6.78, p = 0.01), orienting (R^2 = 0.10, β = 0.32, F(1,61) = 6.76, p = 0.01), and executive conflict (R^2 = 0.54, β = 0.73, F(1,61) = 70.54, p <0.001).

Error rates

With regard to error rates, there was a main effect of cue (Table 3.8); error rate was lower for spatial cue trials relative to no cue trials (p <0.001), and lower for spatial cue than neutral cue trials (p <0.001). There was no difference in error rate for no cue and neutral cue trials (p = 1.00). There was a main effect of target, with a greater error rate for incongruent relative to congruent trials (p <0.001).

The error rate was also greater for incongruent trials relative to congruent trials for each cue type (Figure 3.5); no cue (p <0.001), neutral (p <0.001) and spatial cue trials (p <0.001). There was a significant cue x target interaction (Table 3.8) which was explicable in terms of an orienting effect benefit on error rate; the orienting effect reduced the error rate for congruent trials (0.01, SD: 0.02) relative to the incongruent trials (0.02, SD:0.04) (p <0.01). There was no difference in the effect of alerting on the error rate for incongruent (0.31, SD: 5.07) and congruent trials (0.13, SD: 2.41) (p = 0.53).

Table 3.8. The F value, p value, df and error df for the main effects and interaction effects for the error rate (cue x target) ANOVA (with age^2 as a covariate).

ANOVA factor	**Mean RT (ms)**
cue	F(2,122) = 15.09, p <0.001
target	F(1,61) = 43.47, p <0.001
cue x target	F(1.81, 110.12) = 11.47, p <0.001
age^2	F(1,61) = 9.41, p <0.01
cue x age^2	F(2, 122) = 7.53, p <0.01
target x age^2	F(1,61) = 9.14, p = 0.01
cue x target x age^2	F(1.81, 110.12) = 6.94, p= 0.10

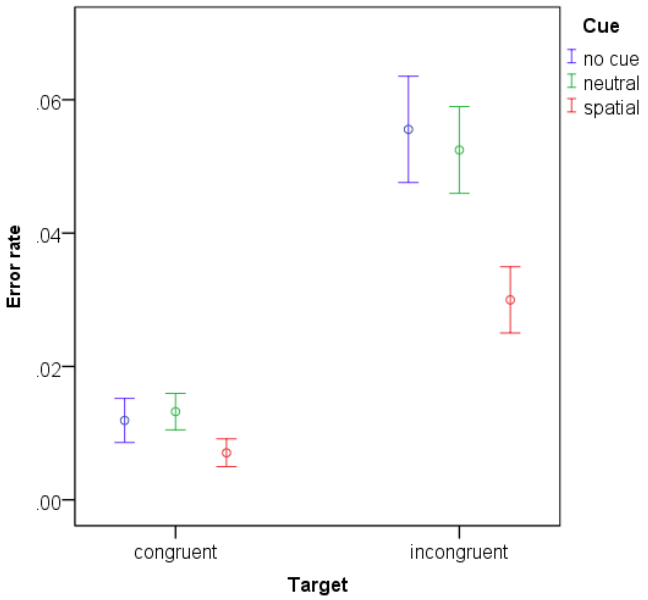


Figure 3.5. Mean error rate (cue x target) for all controls (n=63). Error bars represent ± 1 SE of the mean.

When considering age, there was a significant target x age^2 interaction, with a decrease in incongruent error rate with increasing age^2 (R^2 = 0.15, β = -0.39, F(1,61) = 10.73, p <0.01) (Figure 3.5) which remained significant (p= 0.05) when the outliers depicted in Figure 3.6 were excluded. There was not an association between error rate and age^2 for congruent trials (R^2 = 0.03, β = -0.16, F(1,61) =1.55, p = 0.22). There was also a significant cue x age^2 interaction. There was no association between error rate and age^2 for neutral cue (R^2 = 0.05, β = -0.23, F(1,61) = 3.50, p = 0.07) or spatial cue trials (R^2 = 0.03, β = -0.18, F(1,61) = 2.08, p = 0.16). There was, however, a decrease in no cue error rate with increasing age^2 (R^2 = 0.23, β = -0.48, p <0.001 F(1,61) = 18.22, p <0.001), which remained significant (p <0.01) when an outlier was excluded (Figure 3.7).

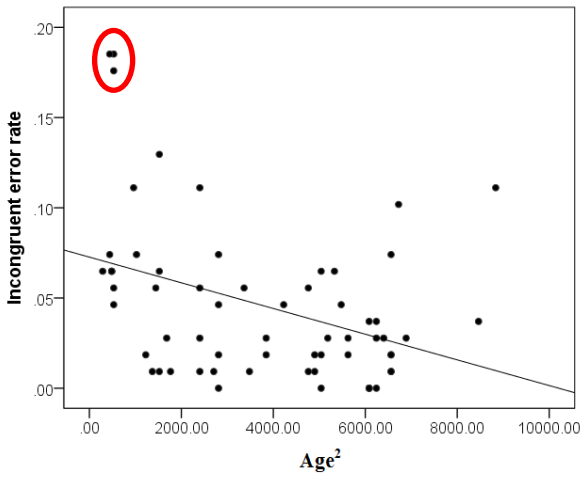


Figure 3.6. Incongruent error rate as a function of age^2 for controls (n=63).
Regression line: y = (-7.12) x + 0.07. The red circle encapsulates three outliers in the data: three young individuals with fast responses.

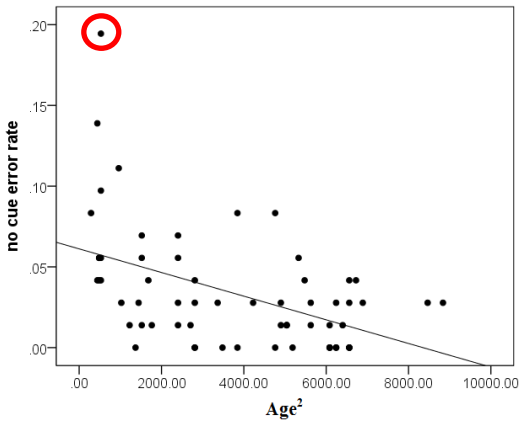


Figure 3.7. No cue error rate as a function of age^2 for controls (n=63).
Regression line: y = (-7.32) x + 0.06. The red circle encapsulates an outlier.

Attentional network independence

There was a significant negative correlation between the alerting and orienting effects (Table 3.9). There were also significant positive correlations between the overall mean RT and the orienting effect, and the overall mean RT and the executive conflict effect.

Table 3.9. Correlation analyses between attentional networks and overall mean RT (*p* values are shown in brackets) for the healthy controls.

	Alerting	**Orienting**	**Executive conflict**	**Correct mean RT (ms)**
controls (n=63)				
Mean RT (covaried for age^2)				
Alerting	-	-.25(.06)*	16 (.21)	.03 (.84)
Orienting	-.25(.06)*	-	.13 (.30)	.35 (.01)*
Executive conflict	.16 (.21)	.13 (.30)	-	.79 (<.001)*

*Correlation is significant at the 0.05 level (2-tailed)

3.4.3 Summary

- Across the whole age range of controls the alerting, orienting and executive conflict effects were significant.
- Across the whole age range of controls there was a negative correlation between the alerting and orienting effects. As with the controls < 45 years old, across the whole age range the overall correct mean RT positively correlated with the orienting and executive conflict effects.
- The size of alerting, orienting and executive conflict effects increased with increasing age^2.
- With regard to error rates, across the whole age range of controls error rates were greater for incongruent trials relative to congruent trials. With increasing age^2 there was a decrease in incongruent error rate.

3.5 Attentional networks in dementia and age-matched controls

3.5.1 Participants

In order to investigate the extent to which attentional network efficiency is differentially affected in dementia patients relative to age-matched healthy controls, the participant cohort comprised 32 LBD patients, 27 AD patients and 21 age-matched healthy controls (over 60 years old). Note that for the healthy control group, only the healthy controls from the CATFieLD study were included in these analyses. Data from the elderly validation study participants was not included to ensure that any differences between the dementia and control groups were not due to differences in the testing procedure; CATFieLD study participants were tested in a controlled clinical environment whilst undergoing EEG, whereas the validation participants were tested in their homes. Furthermore, the CATFieLD controls underwent more detailed clinical work-up and were age, education, and gender matched to the patient groups.

Table 3.10 shows the demographic data for each of the participant groups, and the medication status of the dementia patient groups is shown in Table 3.11. As shown in Table 3.10, all of the groups were well matched with regard to age, gender, and education level. There was no significant difference between the two dementia groups regarding age of onset, and duration of their condition. In terms of global cognitive functioning (assessed using the CAMCOG and MMSE total score), as expected the control group had higher global cognitive functioning scores relative to the dementia groups. However the AD and LBD patients were well matched in terms of global cognitive functioning. With regard to clinically assessed cognitive fluctuations, as expected the LBD group exhibited greater severity of fluctuations relative to the AD group (as shown by the higher CAF and MFS scores). The LBD group also had a higher total NPI score relative to the AD group. As expected, the LBD group scored higher on the UPDRS (total motor subscale score) relative to both the control and AD groups, with no differences in these scores between the AD and control groups. With regard to visual perception, there was no difference between the AD and control groups on the overlapping figures or angle discrimination task, however the LBD group performed worse than the AD group and controls on both visual perception tasks. In terms of medication usage, the vast majority of dementia patients were taking cholinesterase inhibitors, and a substantial proportion of the LBD patients were taking dopaminergic medication. In addition, a proportion of the patients were taking selective serotonin reuptake inhibitors (SSRIs) and antipsychotics (as shown in Table 3.11).

Table 3.10. Demographics (means, and standard deviations in brackets) of the dementia groups (LBD and AD) and age-matched controls. Note: the 'Dementia groups' column shows the results of analyses comparing the AD and LBD groups only.

	Controls (n=21)	**AD (n=27)**	**LBD (n=32)**	**All group comparison**	**Dementia groups (LBD vs. AD)**
Age (years)	76.06 (7.27)	76.15 (7.89)	75.19 (5.98)	$F(2, 88) = 0.18$, $p = 0.84$	$F(1, 57) = 0.28$, $p = 0.60$
Gender (female, male)	7, 14	6, 21	4, 28	$\chi^2(2, N=91) = 4.34$, $p = 0.12$	$\chi^2(1, N=59) = 0.98$, $p = 0.32$
Education level[1]	2.78 (1.01)	2.41 (0.75)	2.34 (0.70)	$F(2, 88) = 2.53$, $p = 0.09$	$F(1, 57) = 0.11$, $p = 0.74$
Condition-age at onset	-	72.74 (7.64)	72.81 (7.04)	-	$F(1, 57) = 0.001$, $p = 0.97$
duration (years)	-	3.43 (2.50)	2.50 (2.00)	-	$F(1, 57) = 2.54$, $p = 0.12$
MMSE[2] total	29.14 (0.85)	21.74 (3.23)	22.19 (3.47)	$F(2,88) = 68.59$, $p < 0.001$*	$F(1,57) = 0.26$, $p = 0.61$
CAMCOG[3] total	96.76 (3.74)	70.48 (11.82)	72.28 (11.26)	$F(2,77) = 48.93$ $p < 0.001$*	$F(1,57) = 0.36$, $p = 0.55$
UPDRS[4] total	1.10 (1.45)	2.33 (2.34)	19.84 (8.30)	$F(2,57) = 104.13$, $p < 0.001$*	$F(1,57) = 112.34$, $p < 0.001$*
NPI[5] total	-	7.15 (6.08)	14.86 (11.64)	-	$F(2,57) = 11.20$, $p < 0.01$*
CAF[6] total	-	0.80 (1.73)	5.56 (4.91)	-	$F(1,55) = 21.84$, $p < 0.001$*
MFS[7] total		8.65 (3.98)	14.59 (5.39)	-	$F(1,56) = 9.84$, $p = 0.01$*
ODFAS[8] total	-	2.42 (3.22)	4.30 (3.57)	-	$F(1,54) = 4.22$, $p = 0.05$
Visuo-perceptual task[9]					
angle discrimination score	18.00 (5.39)	18.81 (2.34)	16.23 (4.50)	$F(2,75) = 2.84$, $p = 0.07$	$F(1,55) = 7.14$, $p = 0.01$*
overlapping figures score	19.75 (0.55)	18.11 (1.91)	15.83 (4.23)	$F(2,73) = 11.56$ $p < 0.001$*	$F(1,54) = 6.62$, $p = 0.01$*

*** $p < 0.05$**, all significant group differences (Bonferroni corrected pairwise comparisons) are detailed on the following page

[1] **Years of education rating scale**: 1 = < 9 years, 2 = 9-11 years, 3 = 12-13 years, 4 = 14+ years

[2] **MMSE = Mini Mental State Examination** (Folstein et al., 1975)

*controls > AD (p<0.001), controls > LBD (p <0.001)

[3] **CAMCOG = Cambridge Cognitive Examination** (Roth et al., 1986)

* controls > AD (p <0.001), controls > LBD (p <0.001)

[4] **UPDRS = Unified Parkinson's Disease Rating Scale** (motor subsection) (Fahn, 1987)

Total: * LBD > controls (p <0.001), LBD > AD (p <0.001)

[5]**NPI = Neuropsychiatric Inventory** (Cummings et al., 1994)

*LBD > AD (p <0.01)

[6]**CAF = Clinician Assessment of Fluctuations** (Walker et al., 2000a)

* LBD > AD (p <0.001)

[7]**MFS = Mayo Clinic Fluctuations Scale** (Ferman et al., 2004)

***** LBD > AD (p <0.001)

[8]**ODFAS = One Day Fluctuation Assessment Scale** (Walker et al., 2000a)

[9]**Visuo-perceptual tasks (Overlapping figures and angels test)** (Mosimann et al., 2004)

Angle discrimination score: ***** controls > LBD (p <0.01), AD > LBD (p = 0.01)

Overlapping figures score: * controls > LBD (p<0.001), AD > LBD (p = 0.01)

Table 3.11. Medication usage of the dementia patient groups

	AD (n=27)	**LBD (n=32)**
cholinesterase inhibitors	25 (93 %)	29 (91 %)
dopaminergic medication	-	21 (66 %)
hours since dopaminergic medication (prior to testing)	-	3.00 (SD: 1.56)
antipsychotics	-	3 (9 %)
SSRIs	3 (11 %)	8 (25 %)

3.5.2 Results

Overall mean RT

Table 3.12 shows the mean RTs of each group for each task condition. For the overall mean RT (across all task conditions) there was a main effect of group ($F(2,74) = 14.78$, $p < 0.001$); controls had a faster mean RT (955.48 ms, S.D: 135.20) relative to LBD ($p < 0.001$) (1546.75 ms, S.D: 307.46) and AD patients ($p < 0.001$) (1292.89 ms, S.D: 309.35), and LBD mean RT was slower than that of the AD group ($p < 0.01$). In the AD group, the overall mean RT negatively correlated with the MMSE ($r = -0.49$, $p = 0.01$) and CAMCOG ($r = -0.46$, $p = 0.02$) total scores. In the LBD group, there was a positive correlation between the overall mean RT and the UPDRS total score ($r = 0.42$, $p = 0.02$).

Table 3.12. Correct **(a)** mean RT (ms) and **(b)** Error rates (%) for each task condition (cue x target), for the controls (> 60 years old), AD and LBD patients. Standard deviations are presented in italics.

Cue	Target	Cohort		
		controls (n=21)	**AD (n=27)**	**LBD (n=32)**
	(a) Mean RT (ms)			
No cue	Congruent	799.67 *(100.36)*	1036.00 *(232.17)*	1326.25 (253.76)
	Incongruent	1226.14 *(217.85)*	1647.56 *(403.54)*	1901.63 *(408.96)*
Neutral	Congruent	794.10 *(89.54)*	1051.26 *(252.55)*	1315.25 *(264.77)*
	Incongruent	1156.57 *(215.70)*	1606.15 *(417.74)*	1876.22 *(430.31)*
Spatial	Congruent	708.52 *(77.93)*	974.67 *(273.33)*	1246.81 *(255.87)*
	Incongruent	1058.24 *(195.53)*	1540.48 (435.57)	1797.19 *(405.60)*
	(b) Error rate (%)			
No cue	Congruent	1.06 *(2.67)*	3.81 *(7.98)*	6.86 *(8.92)*
	Incongruent	2.65 *(3.10)*	15.12 *(11.72)*	21.70 *(12.94)*
Neutral	Congruent	1.32 *(2.08)*	5.04 *(7.35)*	9.20 *(10.71)*
	Incongruent	3.44 *(3.03)*	13.17 *(14.49)*	20.14 *(14.65)*
Spatial	Congruent	0.79 *(1.99)*	5.35 *(9.65)*	7.73 *(8.83)*
	Incongruent	2.12 *(3.16)*	13.68 *(14.54)*	19.79 *(14.88)*

Table 3.13. The F value, *p* value, df, and error df for the repeated measures (cue x target) ANOVA effects with group (controls, AD, LBD) as a fixed factor.

ANOVA factor	**Mean RT (ms)**
cue	$F(2,154) = 58.19,\ p < 0.001$
cue x group	$F(4,154) = 1.94,\ p = 0.11$
target	$F(1,77) = 439.48,\ p < 0.001$
target x group	$F(2,77) = 6.58,\ p < 0.01$
cue x target	$F(2,154) = 7.70,\ p < 0.01$
cue x target x group	$F(4,154) = 0.15,\ p = 0.96$

Table 3.14. Magnitude of the attentional network effects (with standard deviations in italics), calculated using mean RTs, for each group (controls, AD, LBD).

	Cohort		
Network effect	**controls (n=21)**	**AD (n=27)**	**LBD (n=32)**
Alerting	37.57 *(42.39)**	13.07 *(74.02)*	17.70 *(92.85)*
Orienting	91.95 *(36.82)**	71.13 *(85.30)**	73.73 *(107.00)**
Executive conflict	379.52 *(165.14)**	577.67 *(232.56)**	580.00 *(228.68)**

* significant network effect ($p < 0.05$)

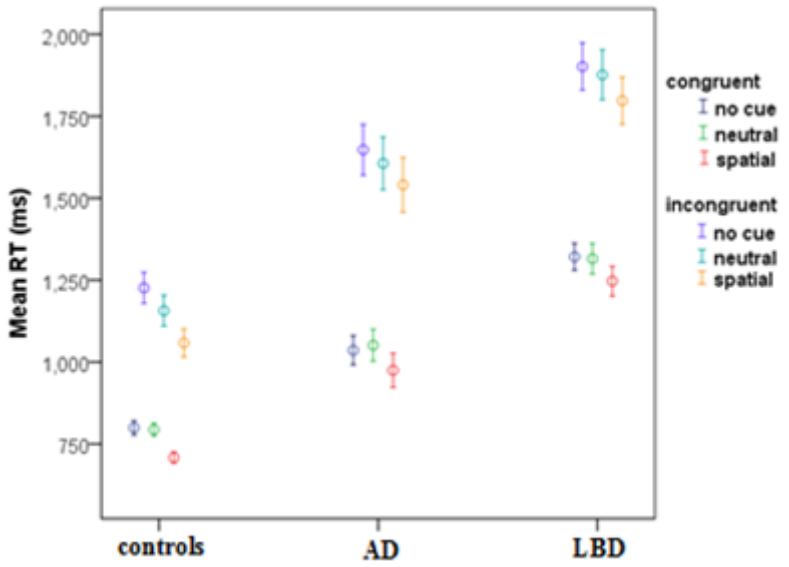


Figure 3.8. Correct mean RT for each task condition (cue x target) as a function of group (controls, AD, LBD). Error bars represent ± 1 SE of the mean.

Attentional network effects

Across all groups there was a main effect of cue (Table 3.13); mean RT for spatial cue trials (1220.99 ms, SE: 33.02) was faster than neutral cue trials (1299.92 ms, SE: 33.02) (p <0.001), and RT for spatial cue trials (1314.91 ms, SE: 30.93) faster than no cue trials (p <0.001). There was no difference in mean RT for neutral cue and no cue trials (p = 0.20). Although the overall cue x group interaction was not significant (Table 3.13), there was possibly a trend in differences between the groups regarding the cueing benefits, and given that *a priori* there might be an expectation of differences between groups in terms of cueing effects (Section 3.1), a post-hoc analysis at the individual group level was performed.

Consistent with previous analyses (sections 3.3 and 3.4), controls had a faster mean RT for neutral cue (975.33 ms, SE: 30.30) relative to no cue trials (1012.91 ms, SE: 31.78), and therefore exhibited a significant alerting effect (p <0.01) (Table 3.14). Controls mean RT for spatial cue trials (883.38 ms, SE: 27.82) was faster than neutral cue trials resulting in a significant orienting effect (p <0.001). In the AD group, the alerting effect was not significant (p = 1.00) as there was no difference between mean RT for neutral (1328.70 ms, SE: 61.41)

and no cue trials (1341.78 ms, SE: 59.03). The AD group mean RT for spatial cue trials (1257.57 ms, SE: 65.98) was faster than neutral cue trials resulting in a significant orienting effect (p <0.001). In the LBD group, there was no difference between mean RT for neutral (1595.74 ms, SE: 71.37) and no cue trials (1613.44 ms, SE: 65.72) and thus the alerting effect was not significant (p = 1.00). LBD spatial cue RT (1522.00 ms, SE: 56.24) was faster than neutral cue RT resulting in a significant orienting effect (p <0.01). Although the alerting effect was not significant in the dementia groups, the groups (controls, AD, LBD) did not differ significantly with respect to the magnitude of the alerting effect (F(2,77) = 2.34, p = 0.10), or the orienting effect (F(2,77) = 0.40, p = 0.67) (Figure 3.9).

There was a main effect of target (Table 3.13) due to greater mean RTs for incongruent trials relative to congruent trials. Controls had a greater mean RT for incongruent trials (1146.98 ms, SE: 45.17) relative to congruent trials (767.43 ms, SE: 18.90), and thus a significant executive conflict effect (p <0.001). The AD group had a longer mean RT for incongruent trials (1598.06 ms, SE: 79.23) relative to congruent trials (1020.64 ms, SE: 47.54) and therefore the AD executive conflict effect was also significant (p <0.001). An executive conflict effect was also evident in the LBD group (p <0.001); patients' mean RT for incongruent trials (1858.34 ms, SE: 72.13) was greater than that of congruent trials (1296.10 ms, SE: 43.47).

The target x group interaction (Table 3.13) was due to a significant effect of group with respect to the executive conflict effect magnitude (F(2,77) = 6.64, p <0.01), with the conflict effect being smaller in controls relative to AD (p = 0.01) and LBD (p <0.01). However, there was no difference in the magnitude of the executive conflict effect between AD and LBD patients (p = 1.00).

A significant cue x target interaction, independent of group, was also evident (Table 3.13). Mean RT was greater for incongruent trials relative to congruent trials for each cue condition; no cue (p <0.001), neutral (p <0.001) and spatial cue (p <0.001). The alerting benefit (across all groups) was significantly smaller for congruent target trials (18.41, SD: 117.58) relative to incongruent trials (42.40, SD: 109.73) (p <0.01). There was no difference in the size of the orienting effect for congruent (75.69, SD: 101.10) and incongruent trials (79.59, SD: 132.75) (p = 0.83).

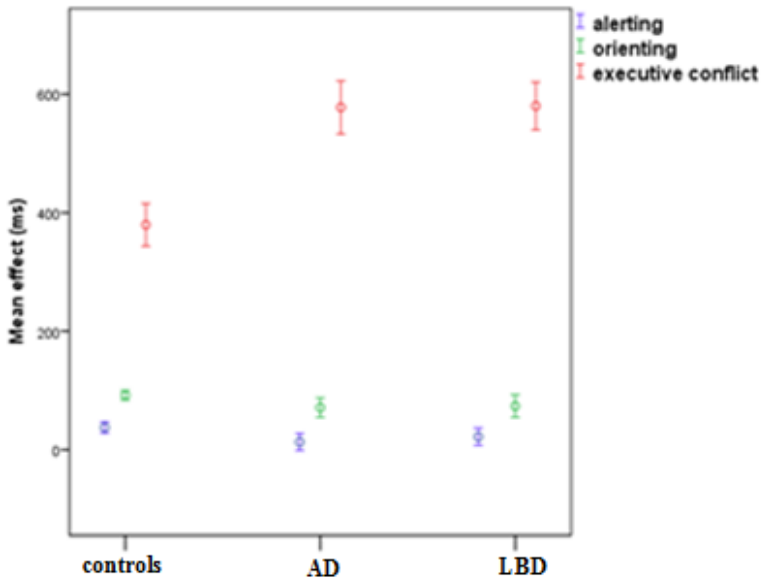


Figure 3.9. Mean attentional network effect (alerting, orienting, executive conflict) as a function of group. Error bars represent ± 1 SE of the mean.

Error rates

With regard to error rates, there was a significant target x group interaction (Table 3.15) which is evident from Figure 3.10. For all three groups the error rate was greater for incongruent target trials relative to congruent trials. For congruent trials there was no difference in the error rate of the control and AD groups (p = 0.26), or AD and LBD groups (p = 0.29). However, LBD congruent error rate was greater than that of the controls (p <0.01). For incongruent trials, error rate was lower in controls relative to both the AD (p <0.01) and LBD groups (p <0.001). There was a non-significant trend for a higher incongruent error rate in the LBD group relative to the AD group (p = 0.10).

Table 3.15. The F value, *p* value, df, and error df for the error rate (cue x target) ANOVA effects, with group as a fixed factor (controls, AD, LBD).

ANOVA factor	Error rates
cue	$F(2,152) = 4.11,\ p = 0.20$
cue x group	$F(4, 152) = 0.45,\ p = 0.78$
target	$F(1,76) = 1.02,\ p = 0.32$
target x group	$F(1,76) = 10.27,\ p < 0.001$*
cue x target	$F(2,152) = 2.55,\ p = 0.80$
cue x target x group	$F(4,152) = 0.86,\ p = 0.49$

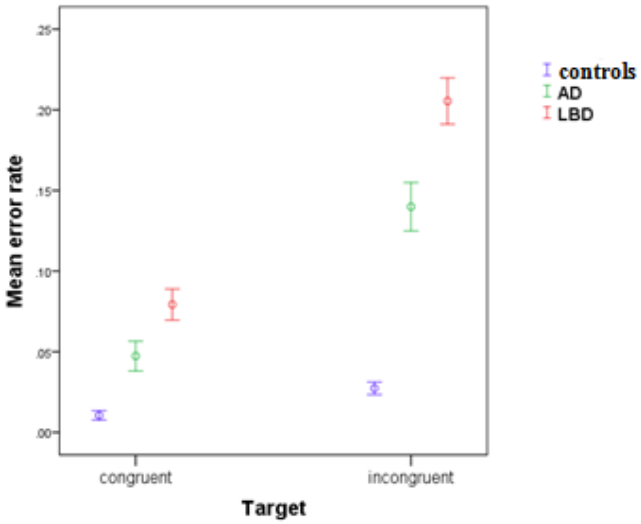


Figure 3.10. Mean error rate as a function of target condition for each group. Error bars represent ± 1 SE of the mean.

Correlates of total error rate

There were negative correlations between the total error rate and total MMSE score in the AD ($r = -0.46$, $p = 0.02$) and LBD ($r = -0.54$, $p < 0.01$) groups. There were also negative

correlations between the CAMCOG total sore and the total error rate in the AD (r = -0.50, p = 0.01) and LBD (r = -0.57, p <0.01) groups.

Attentional network independence

Table 3.16 shows that whilst the AD group exhibited independent attentional network effects, there was a negative correlation between the alerting and orienting effects in the controls and LBD patients. In all three groups there was a positive correlation between the executive conflict effect and overall mean RT.

Table 3.16. Correlation analyses between the attentional networks and overall mean RT (across all task conditions) for each group (p values are shown in brackets)

	Alerting	**Orienting**	**Executive conflict**	**Correct mean RT (ms)**
controls (n=21)				
Alerting	-	-.44 (.05)*	.11 (.65)	.15 (.50)
Orienting	-.44 (.05)*	-	.17 (.48)	.30 (.18)
Executive conflict	.11 (.65)	.17 (.48)	-	.79 (<.001)*
AD (n=27)				
Alerting	-	-.13 (.53)	-.14 (.50)	-.19 (.34)
Orienting	-.13 (.53)	-	.02 (.93)	-.24 (.14)
Executive conflict	-.14 (.50)	.02(.93)	-	.74 (<.001)*
LBD (n=32)				
Alerting		-.52 (<.01)*	-.16 (.38)	-.32 (.07)
Orienting	-.52 (<.01)*		.13 (.47)	.13 (.48)
Executive conflict	-.16 (.38)	.13 (.47)	-	.76 (<.001)*

*Correlation is significant at the 0.05 level (2-tailed)

3.5.3 Summary

- Overall mean RT was slower in the dementia groups (AD and LBD) relative to the controls. LBD overall mean RT was slower than that of AD.
- The alerting effect was significant in the controls but not the dementia (AD and LBD) groups. The orienting and executive conflict effects were significant for all three groups.
- With regard to the magnitude of the attentional network effects, there was no difference between the groups for the alerting and orienting effects. The executive conflict effect was greater (indicative of reduced ability to resolve conflict) in the dementia groups (AD and LBD) relative to the control group.
- The LBD group had a greater error rate for congruent and incongruent trials relative to the controls. The AD group error rate for incongruent trials was greater than that of the control group.
- The LBD and controls groups exhibited a negative correlation between the alerting and orienting effects, whereas the AD group exhibited independent attentional networks. In all three groups the overall mean RT positively correlated with the executive conflict effect.

3.6 Discussion

3.6.1 Validation of the modified ANT

The validation analyses reported in this chapter showed that the modified ANT elicited significant alerting, orienting and executive conflict effects in a cohort of young healthy individuals. Comparable to the findings reported by Fan et al. (2002), the attentional network effects observed in our young healthy cohort were uncorrelated, supporting the notion of independence of the attentional networks, at least in young healthy individuals.

With regard to the size of the attentional network effects, in our young healthy cohort the magnitude of the orienting effect elicited by the modified ANT was comparable to the orienting effect reported by Fan et al. (2002). The magnitude of the alerting effect, however, was smaller than that reported by Fan et al. (2002). It is likely that this was due to the design

modifications of our task relative to the original ANT. As discussed in chapter 2, our task design incorporated longer cue-target intervals relative to the original ANT to account for slower cognitive processing speed exhibited by elderly individuals relative to young adults (Hoogendam et al., 2014), therefore optimising the task design for elderly and dementia cohorts. A potential consequence of this longer cue-target interval is less cueing benefit, which may explain the diminished alerting effect observed when using our modified ANT. Our modified ANT had, on average, a longer cue-target interval (1800 ms) relative to the Fan et al. (2007) version of the task (described in chapter 1, section 1.5.1) which had an average cue-target interval of 550 ms. In our young healthy cohort, the executive conflict effect elicited by the modified task was of a greater magnitude than that reported in previous ANT studies (Fan et al., 2007; Fan et al., 2002). This greater executive conflict effect is indicative of less efficient resolution of conflict, and this is explicable in terms of increased executive processing complexity in our modified task relative to the original ANT (as discussed in chapter 2).

3.6.2 Attentional networks in healthy ageing

The analyses conducted using the full age range of healthy participants (aged 17- 94 years) showed that with increasing age there was an increase in overall mean RT (across all task conditions). This positive relationship was linear when age was modelled as age^2. These findings fit with the extensive literature documenting reaction time slowing with increasing age (Der & Deary, 2006; Fozard et al., 1994; Woods et al., 2015), which may be explicable in terms of an age-related decline in processing speed (Salthouse, 1996).

Across the whole age range, the modified ANT elicited significant alerting, orienting and executive conflict effects. This is indicative of our modified ANT being valid across a wide age range of healthy individuals. There was an increase in the magnitude of each of the attentional network effects (alerting, orienting, executive conflict) with increasing age^2; this is suggestive of greater alerting and orienting benefits, but reduced executive conflict processing efficiency, with increasing age. Whilst several studies have reported a diminished alerting effect (as opposed to an enhanced effect) with increasing age (Gamboz et al., 2010; Jennings et al., 2007; Noh et al., 2012), Fernandez-Duque and Black (2006) reported an

increased alerting effect with increasing age. There is substantial variability in the findings of existing literature pertaining to attentional network efficiency in healthy ageing (described in section 3.1), which is likely due to heterogeneity with regard to task design and participant cohorts.

In addition, there was a cue x age^2 interaction which was due to a greater rate of RT increase with increasing age^2 for no cue trials relative to neutral and spatial cue trials. This is suggestive of the older participants still being able to make use of the cues in a beneficial way; the cueing stimuli may help overcome some of the age-related deficits which result in slower RTs during the no cue condition. Therefore it is likely that the increased alerting effect with increasing age was mainly due a decreased ability to respond during the no cue condition as opposed to the neutral cue having a more beneficial effect in the older individuals (i.e. the cues had a compensatory effect for the slowing in the absence of a cue). However, given that the rate of RT increase with increasing age was comparable for the neutral and spatial cue conditions, this compensatory explanation does not adequately account for the increased orienting effect with age. Comparable to our task, Deiber et al. (2013) used a longer cue to target interval (fixed duration, 1600 ms) relative to the original ANT, and also found an increased orienting effect in elderly individuals. It is therefore possible that when the cue to target interval is longer the cueing stimuli are more beneficial for older individuals, thus resulting in increased alerting and orienting effects in older individuals.

With regard to the target stimuli, the rate of mean RT increase with increasing age^2 was greater for incongruent trials relative to congruent trials. This explains the greater executive conflict effect with increasing age, which is suggestive of ageing being associated with reduced conflict processing efficiency. Given that prefrontal cortex deterioration is a prominent feature of healthy ageing (Hedden & Gabrieli, 2004), which is a key region of the executive conflict network (Fan et al., 2005), it is postulated that this may be a contributory factor underlying the age-related executive conflict deficits. Furthermore, reduced efficiency of the executive conflict network fits with the extensive literature documenting an age-related decline in performance in frontally dependent tasks of executive functioning such as the Stroop task (Bryan & Luszcz, 2000).

Although the young healthy participants exhibited independent attentional networks, when the whole age range of healthy participants was analysed the networks were no longer

independent; there was a negative correlation between the alerting and orienting networks. Whilst the attentional networks have been shown to be anatomically separable (Fan et al. (2005), it has been suggested that there is functional overlap of the networks (Raz & Buhle, 2006). As described in section 3.1, several studies using modified versions of the task have reported behavioural interactions of the networks, such as alerting enhancing the orienting effect (Callejas et al., 2004; Fuentes et al., 2010); it has been suggested that network interactions may produce efficient and adaptive behaviour (Callejas et al., 2004). As discussed in chapter 2 (section 2.5), in order to ensure our modified ANT was suitable for use with neurophysiological recordings, the design of our task was analogous to the version of the ANT used by Fan et al. (2007) (described in chapter 1, section 1.5). As Fan et al. (2007) also reported a negative correlation between the behavioural alerting and orienting effects, it is likely that this association between the two networks was due to the design of the task, as opposed to our specific participant cohort. Our modified ANT, and the version of the ANT used by Fan et al. (2007), had three cues (no cue, neutral, spatial) as opposed to four cues (no cue, centre, double, spatial) which were used in an earlier version of the ANT (Fan et al., 2002). For our modified ANT (and the version of the ANT used by Fan et al. (2007)) the alerting and orienting effects were calculated using a common factor: the mean RT for neutral cue trials. However, the alerting and orienting calculations used in the early version of the ANT by Fan et al. (2002) did not share this common factor; the alerting effect was calculated by contrasting the no cue and double cue mean RT, whilst the orienting effect was the contrast between the centre cue and spatial cue mean RT. It is therefore likely that the association between the alerting and orienting network effects evident in healthy controls when using the modified ANT was due to the shared cue in the network calculations. This association between the alerting and orienting networks was not evident in the young healthy cohort, however it is possible that a statistical correlation between these networks was harder to evidence in the younger individuals as they exhibited less variability of the alerting and orienting effects relative to the older individuals.

Across the whole age range, there was a positive correlation between the overall mean RT and executive conflict effect, indicative of reduced conflict processing being associated with slower RTs; this was as expected given that this correlation has also been found when using the original ANT (Fan et al., 2002). However, there was also a positive correlation

between the orienting effect and overall mean RT which was also evident in the young healthy cohort (under 45 years old). This association was not evident with the original ANT (Fan et al., 2002; Fan et al., 2007), therefore it is likely that this was due to the task design modifications. It is possible that there is a 'cost' associated with having a distracting neutral cue, whereby attention is focussed on the centrally located flashing box as opposed to the more peripheral location of the subsequent target appearance; during the neutral cue condition an element of re-orientation to the target is required. The positive correlation may therefore be explicable in terms of the slower responders being less able to readjust their attention following the neutral cue.

In terms of response error rates, across the whole age range the healthy participants exhibited greater error rates for incongruent target trials relative to congruent target trials; this was as expected given the additional level of executive processing complexity associated with the incongruent target trials, and fits with the findings of previous ANT studies (Fan et al., 2007; Fan et al., 2002; Macleod et al., 2010). With increasing age, there was decrease in the incongruent error rate, as well a decrease in the no cue error rate (averaged across congruent and incongruent trials). Whilst there was an increase in overall mean RT with increasing age, the decrease in error rate for the most complex task situations (as no cue is the absence of a stimulus, and incongruent trials require greater conflict processing relative to congruent trials) is suggestive of a speed accuracy trade off; the older individuals were slower yet less error prone for the more taxing task conditions relative to the younger adults. It is postulated that activation of the corticostriatal network is necessary for threshold adjustment of the speed accuracy trade off, and given that elderly adults have been found to have reduced integrity of white matter corticostriatal connectivity, it has been suggested that this may be a contributory factor underlying the more conservative speed accuracy trade off exhibited by elderly adults (Forstmann et al., 2011).

3.6.3 Attentional networks in dementia and age-matched healthy controls

The results of the analyses to compare task performance in the dementia groups and age-matched controls showed that both dementia groups (AD and LBD) were slower than the controls with regard to overall mean RT (across all task conditions), and the LBD group was slower than the AD group. These findings are comparable to previous ANT studies of

dementia cohorts (Fernandez-Duque & Black, 2006; Fuentes et al., 2010). Given that in the LBD group a greater overall mean RT was associated with a higher UPDRS total score, the slower mean RT exhibited by LBD patients relative to the AD patients is likely due to the impaired motor functioning and bradykinesia of the LBD patients. In the AD group, the negative correlation between the overall mean RT and total scores on global cognitive function measures (MMSE and CAMCOG) is indicative of an association between RT slowing and diminished global cognitive functioning. Ballard et al. (2001) reported increased RTs (during a choice RT task) to be associated with reduced global cognitive functioning (as measured by the MMSE) in both AD and DLB patients, however their DLB cohort was on average more cognitively impaired (mean MMSE score: 17.3, SD: 4.6) relative to our DLB patients (mean MMSE score: 22.19, SD: 3.47), which may explain the lack of an association between mean RT and global cognitive functioning in our DLB patients. In addition, PDD and DLB patients exhibiting RT fluctuations (variability in a choice RT task) have been found to have slower RTs and a tendency towards lower MMSE scores relative to non-fluctuators (Ballard et al., 2002). Given these reported associations between behavioural measures of attentional performance and MMSE scores in AD and LBD patients, and the association between mean RT and global cognitive functioning in our AD group, MMSE and CAMCOG scores were considered as covariates during the attentional network analyses, however no significant effects or interactions were observed.

With regard to the attentional network effects, the alerting effect was significant in the elderly controls, but was not significant in either of the dementia groups. However, in terms of the magnitude of this alerting effect there were no differences between the groups; this is likely due to the greater alerting effect standard deviation in the dementia groups relative to the controls. As discussed in section 3.1, the existing literature on attentional network efficiency in dementia cohorts is very limited; to date there are only two such published studies. Whilst there is heterogeneity between the studies (in terms of methodologies, task design and participant cohorts), our modified task was comparable to the task design used by Fernandez-Duque and Black (2006) (described in Table 3.2) in terms of cueing stimuli; both tasks used flashing boxes as opposed to central asterisks for the cues, and therefore used more peripheral cueing relative to the original ANT. In this study, Fernandez-Duque and Black (2006) observed a significant alerting effect in AD patients which was comparable to age-

matched controls, however the mean MMSE of their AD cohort (24.3, SD: 2.5) was greater than that of our AD patients (21.74, SD: 3.25). Although the alerting effect did not correlate with the MMSE score in our AD cohort, it is possible that heterogeneity of the participant cohorts may explain the disparity between the AD alerting effect findings in our cohort and that of Fernandez-Duque and Black (2006).

In an fMRI study of the attentional networks in the CATFieLD participant cohort, Firbank et al. (2015) also reported a lack of a behavioural alerting effect in the dementia groups, however all groups (LBD, AD, controls) exhibited comparable fronto-parietal-occipital activations associated with alerting effect. These functional activation findings suggest that the absence of a behavioural alerting effect in the dementia groups is not due to region-specific functional deficits of the alerting network. The alerting network has been shown to be modulated by the noradrenergic system (Fan et al., 2005), thus it is possible that reduced integrity of the noradrenergic system may be a contributory factor underlying the lack of alerting effect observed in the dementia groups.

Given that the orienting network has been suggested to be modulated by the basal forebrain cholinergic system, which is markedly affected in LBD patients, it was hypothesised that the LBD patients would exhibit reduced orienting efficiency relative to the age-matched controls, however this hypothesis was not supported. The orienting effect was found to be significant in all three groups. When the groups were compared in terms of the magnitude of the orienting effect, there were no significant differences between the groups. The patients were taking a variety of medication including cholinesterase inhibitors; this medication confound is highly salient given that the orienting network is postulated to be modulated by the cholinergic system (Fan et al., 2005). However, when medication usage was added as a covariate in the attentional network analyses models there were no significant effects on the findings, and thus it is unlikely that the observed orienting effects in the patients were explicable in terms of medication usage.

The orienting effect observed in the AD patients is comparable to previous literature showing preservation of orienting network efficiency in AD patients (Fernandez-Duque & Black, 2006). Fuentes et al. (2010) found LBD patients to exhibit reduced orienting efficiency in the absence of an alerting cue, however the version of the ANT used in this study was substantially modified relative to the original task; their modified version of the ANT was

designed to probe the interactions of the attentional networks, and included an auditory 'alerting' cue (as detailed in Table 3.2). The authors reported that in the absence of an initial 'alerting' tone the DLB group were unable to maintain the necessary level of alertness to exhibit significant orienting and executive conflict effects. As the Fuentes et al. (2010) version of the task used multisensory cueing stimuli (both auditory and visual), it is feasible that their task probed different facets of attention relative to our modified ANT.

In both dementia groups (AD and LBD) the magnitude of the executive conflict effect was greater than that of the age-matched control group, indicative of reduced ability to resolve conflict in the dementia groups (irrespective of dementia type). This fits with existing literature showing reduced efficiency of the executive conflict network in AD patients (Fernandez-Duque & Black, 2006), and more broadly the extensive literature documenting executive functioning deficits in AD (McGuinness et al., 2010). Executive functioning deficits have also been shown to be characteristic of LBD patients (Noe et al., 2004). Given that the executive conflict network is postulated to be modulated by the dopaminergic system (Fan et al., 2005), the reduced executive conflict efficiency observed in the LBD patients fits with the notion of dopaminergic mediated frontal-striatal dysfunction being a contributory factor underlying executive dysfunction in LBD (Kehagia et al., 2013).

In terms of error rates, in both dementia groups there were negative correlations between the total error rate (across all task conditions) and clinical measures of global cognitive functioning (MMSE and CAMCOG total score), which is indicative of the more cognitively impaired patients being prone to more task errors. The AD group had a greater error rate for the incongruent trials relative to the control group, whereas relative to the controls the LBD group had a greater error rate for both the congruent and incongruent trials. These error rate findings, in conjunction with the attentional network effects, are suggestive of the LBD patients performing at a comparable level to the AD group (as they had comparable attentional network effects) whilst they were engaged in the task, however the LBD group were more prone to errors (loss of engagement in the task) in the target condition which requires less conflict processing. Therefore, from the perspective of these behavioural findings, the LBD group did not exhibit disease specific deficits in the attentional networks whilst engaged in the task; instead they appeared to be prone to a greater degree of loss of task engagement. Whilst it is possible that task errors may reflect cognitive fluctuations, there

were no associations between error rates and clinically assessed cognitive fluctuations in the LBD cohort.

There were no associations between the ANT behavioural data (network effects, mean RT, error rates) and cognitive fluctuations in our LBD patient cohort. Whilst Walker et al. (2000b) reported correlations between RT measures in DLB patients and clinically assessed cognitive fluctuations, it was within-subject RT variability (SD) during a simple choice RT task and a vigilance task which they found to positively correlate with cognitive fluctuation severity. In addition to the RT analyses reported in this chapter, I conducted analyses using within-subject SD for the ANT measures, however there were no correlations between this RT variability data and LBD group cognitive fluctuations. Whilst the ANT incorporates elements of a choice RT task, the combination of cue and target stimuli means that the ANT involves more complex fronto-executive processing relative to simple choice RT tasks, which may explain the lack of association between the ANT measures and cognitive fluctuations. Furthermore, the DLB cohort in the Walker et al. (2000b) study had a mean MMSE score of 17.6 (SD: 5.1) and thus were more cognitively impaired relative to our LBD cohort who were only mildly impaired (MMSE score: 22.19, SD: 3.47).

The results discussed throughout this chapter were calculated using participants' mean RTs across all trials, as opposed to analysing the behavioural data for each individual trial. Analysing the task data on a trial by trial basis however would provide a useful indicator of RT variability, and may be more likely to associate with cognitive fluctuation severity. A method which has been devised in order to measure RT variability is the use of the Ex-Gaussian distributions, which involves fitting the empirical RT data to an Ex-Gaussian (exponentially modified Gaussian distribution) which is calculated using tau and mu tail parameters; the 'slow' tail (tau) has been found to be an effective indicator of cognitive processing efficacy (Nilsson, Thomas, O'Brien, & Gallagher, 2014; Schmiedek et al., 2007). It would therefore be of interest to investigate whether there is an association between Ex-Gaussian tau tails in the LBD patients and cognitive fluctuation severity.

3.6.4 Limitations

As discussed in the methods section, the results presented in this chapter were calculated using absolute mean RT data. Given that the dementia groups exhibited slower overall mean RTs relative to the age-matched controls, it is possible that this slowing could be due to a reduction in overall processing speed, which may potentially contribute to the observed attentional network deficits in the dementia groups. A method which has been used in previous ANT studies in an attempt to control for overall processing speed is normalisation of RTs, whereby the RT for each task condition (cue and target) is divided by the participants' overall mean RT. A number of ANT studies using various cohorts (described in Tables 3.1 and 3.2) have found normalised data to yield comparable results to the absolute (non-normalised) RT data. Fernandez-Duque and Black (2006) found that in AD patients normalised and absolute RT data yielded the same pattern of results, suggestive of the attentional network effects observed in the dementia patients not just being due to processing speed abnormalities. Furthermore, although the results are not included in this chapter, preliminary analyses were also conducted using normalised RTs; importantly, the results of these preliminary analyses did not differ substantially from the non-normalised results. It is therefore reasonable to assume that the changes in the attentional networks in healthy ageing and dementia reported in this chapter were not merely due to differences in overall processing speed between the groups.

An additional limitation is that the healthy control participants were recruited for two different studies (CATFieLD and the validation study), and were therefore assessed under different testing conditions. Most notably, the CATFieLD control participants completed the ANT whilst simultaneously undergoing EEG recordings, whereas the validation study participants did not undergo EEG. As discussed, in order to avoid potential confounds associated with differences in testing procedures between the studies, only the CATFieLD study healthy controls were used as age-matched controls for the dementia group analyses. However, for the healthy ageing analyses all control participants (from both studies) were included. As all of the young control participants in this analysis were from the validation study only, it is possible that that the differences in testing procedure between the young and older controls may have had an impact on the results of this analysis.

With regard to the task design, the modified ANT was designed to assess the same attentional networks as the original ANT; however there were disparities between our modified task and the original ANT with respect to task stimuli. Whilst this is not a limitation *per se*, it does mean that the extent to which the findings reported in this chapter can be compared to previous ANT literature is limited. Following the presentation of the target stimuli, for our modified ANT the task was to indicate the direction in which the majority of arrowheads were facing (as opposed to the direction of the central arrow in the original ANT), consequently the two versions of the task do not necessarily probe the same facet of executive function. The modified ANT also entails a degree of numerosity processing as participants had to decipher the direction in which the majority of arrowheads were facing. This numerosity aspect of the task is of interest when assessing dementia patients given that subitising has been shown to be dependent upon integrity of the right temporo-parietal junction (Ansari et al, 2007; Papeo et al, 2010), which has also been implicated in both AD (Frisoni et al., 2005) and DLB pathophysiology (Metzler et al, 2010). It is therefore possible that the increased executive conflict effect evident in the dementia groups, indicative of reduced efficiency of the executive conflict network, may in part be explicable in terms of difficulties with numerosity processing in the dementia patients. Future imaging studies using the modified ANT may be helpful in examining this.

From this behavioural data alone, it is not possible to deduce the extent to which the attentional network differences between the groups were explicable in terms of differences in cognitive processing speed or motor slowing. In order to further investigate the processes underlying the aberrant attentional network effects in the dementia groups, the oscillatory activity associated with each of the attentional networks was investigated using EEG; this is described in detail in the following chapters (chapters 4-8).

Chapter 4 . EEG pre-processing methodology

This chapter provides an overview of the methodologies associated with the analysis of the EEG data, with particular focus on the pre-processing steps implemented. Firstly, a summary of general methodological considerations associated with analysis of EEG data is given, and this is followed by in-depth description of each of the pre-processing steps conducted. Finally, each of the EEG analysis techniques implemented (detailed in subsequent chapters) are briefly discussed.

4.1. Methodological considerations

EEG has potential to provide extensive insight into brain functioning and cognitive processes. In recent years, due to the development and ubiquity of neuroimaging techniques, the use of EEG in dementia research has somewhat fallen out of favour. However it is important to acknowledge the value of EEG for dementia research; as discussed in chapter 1, EEG offers superior temporal resolution relative to neuroimaging techniques, and the non-invasive nature of the technique makes it ideal for acquiring neurophysiological data from dementia cohorts.

EEG recordings contain a plethora of information; raw EEG signals are a mixture of hundreds of different sources of neuronal activity (Luck, 2005), as well as non-cortical (artefactual) activity. The challenge when conducting EEG research is to devise an appropriate analysis method to extract the signal of interest (cortical activity) from the raw data. Whilst some consensus is evident amongst the EEG community regarding appropriate analysis procedures, particularly what should be done at the pre-processing stage, the vast assortment of techniques which have been developed to aid this process has resulted in substantial heterogeneity in the methods used to analyse EEG. An inevitable consequence of this is that there is a degree of subjectivity involved in the selection and application of methods used for EEG analyses (van Diessen et al., 2014). Whilst an in-depth discussion regarding the diverse and largely subjective nature of EEG analysis is beyond the scope of

this chapter, the objective of the present chapter is to provide a detailed overview of the devised analysis method, and the rationale for using each technique will be discussed in subsequent sections.

4.2 Pre-processing methodology

Pre-processing is a crucial step in analysing EEG data; without this step raw EEG recordings (see Figure 4.1) are largely uninformative as the data often contains a substantial amount of noise (artefactual activity). Artefacts which are frequently evident in EEG data include: movement artefacts, noise from AC power lines, eye-blinks and noisy electrodes (for example due to the contact with the scalp being lost). The purpose of performing a series of pre-processing steps is to remove such artefacts in order to increase the signal-to-noise ratio of the recordings, thus enabling the cortical activity of interest to be investigated. Ideally, EEG data should be acquired so that noise in the recordings is negligible; however noisy data is an inevitable consequence of working with elderly individuals with dementia as they often find it difficult to remain seated in the same position for an extended period of time, resulting in movement artefacts in the data. This issue of noise in the data is particularly pertinent when assessing dementia patients with parkinsonism; a 4-6 Hz resting tremor is characteristic of DLB (Onofrj et al., 2013). It was therefore essential to apply a series of pre-processing steps to our data to ensure that the subsequent analyses results were meaningful and interpretable (and not merely due to the presence of excess noise in the data).

The pre-processing steps which were implemented are discussed in subsequent sections, in the order in which they were applied to the data. Each participant's data was analysed separately (as opposed to batch processing of the data); this is common practice in the pre-processing of EEG data, and was necessary given that several of the steps required visual inspection of each individual's data (discussed in subsequent sections). Each of the pre-processing steps were conducted in succession for an individual participant's data (prior to the next participant's data being analysed). Participants' data were analysed in a random order, i.e. each participant's data were randomly selected from all participants' data (controls and dementia patients); this was done to avoid potential subjective interpretations of the data

on a particular day/week the data was analysed (to avoid potentially biasing the processing of one particular group). It was not possible to be blind to the diagnosis of the participants; when visually inspecting the raw data it was usually apparent which individuals had dementia due to the presence of a greater number of movement artefacts. To check for consistency in the pre-processing of participants' data, I selected ten participants (both controls and dementia patients) randomly and re-processed their data. Upon re-processing, the same artefactual epochs (section 4.2.4) were removed and the same independent components rejected (section 4.2.6), indicating that there was consistency in the pre-processing approach for the steps which involved a degree of subjectivity.

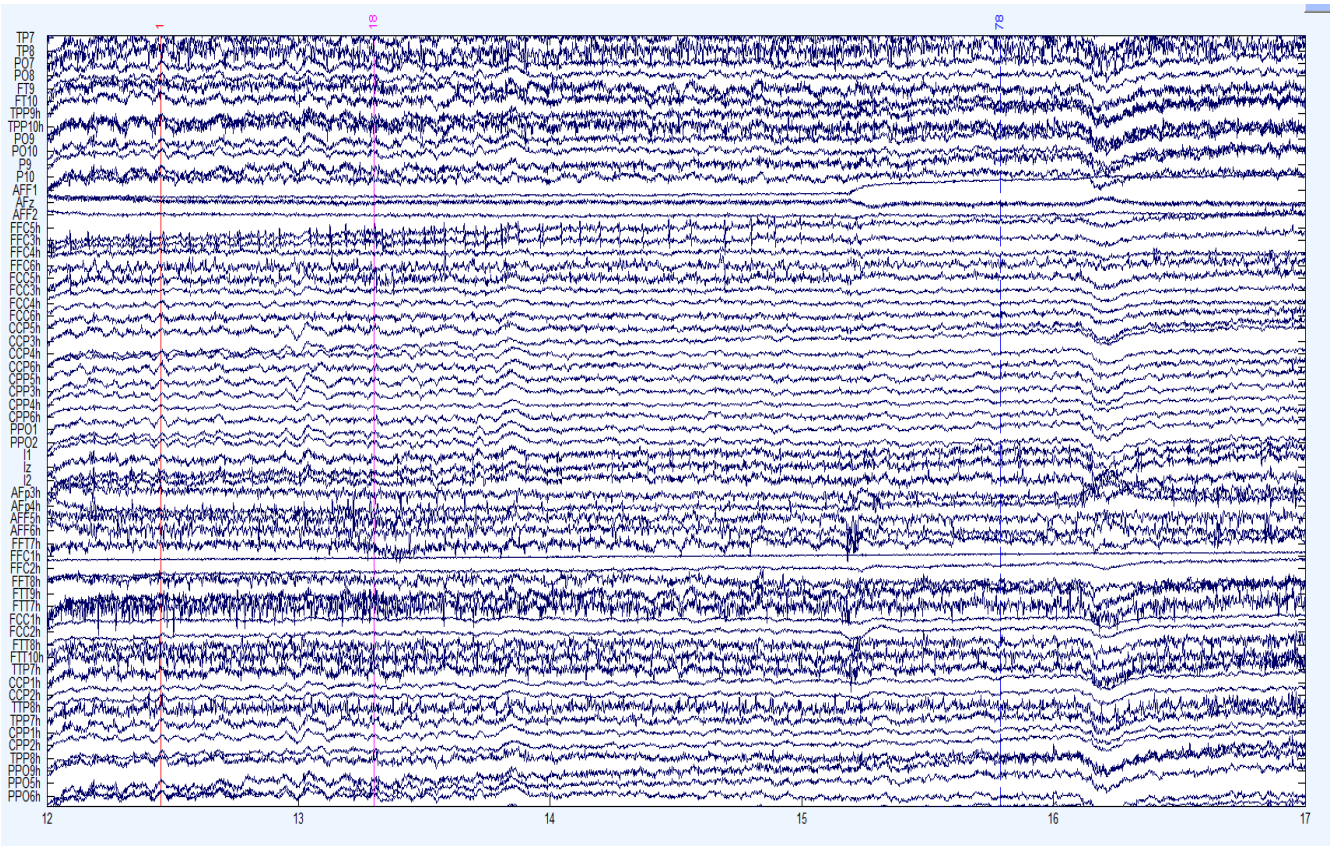


Figure 4.1. Example of one participant's raw EEG recording (continuous data prior to pre-processing) depicted in the time domain (the x axis indicates time (ms)). For each participant raw signals were recorded from each of the 128 channels (Y axis). The vertical lines indicate time points at which a task trigger occurred (ANT task stimuli, and participant responses).

4.2.1 Filtering the data

Filtering is a commonly used EEG pre-processing step. The theory underpinning the application of digital filters to EEG data is that by attenuating certain frequencies it is possible to increase the signal-to-noise ratio of the data. Whilst it is acknowledged that filtering EEG data leads to distortion of the signal, particularly in the time domain (Luck, 2005; Vanrullen, 2011), this controlled distortion can be minimised by selecting a carefully designed filtering technique which is appropriate for the data and the scientific questions being addressed (Widmann & Schroger, 2012). Application of an appropriate filter can greatly reduce the noise in the signals with minimal temporal distortion, enabling identification of cortical signals (Lopez-Calderon & Luck, 2014; Luck, 2005). To clarify the reasons for which specific filters, and filter parameters, were applied to my data, a brief description of each category of filter is given below:

High pass filter

High pass filters attenuate low frequencies in the EEG signal, and they are primarily used to remove voltage drifts in the data which can distort ERP waveforms (Luck, 2005). Slow voltage drifts can be caused by head movements, skin potentials (e.g. caused by sweating) and drift in electrode impedance. High-pass filters with a cut-off frequency of 1 Hz have been shown to reduce the amplitude of ERPs (Widmann & Schroger, 2012), therefore Luck (2005) recommends using a cut off value of 0.01 Hz for healthy participants' data. For my data, a high-pass cut off value of 0.1 Hz was used as this is suggested as an appropriate value to use when working with patients (Luck, 2005), especially with patients who have difficulty remaining still, as excessive movement during recordings can result in low frequency voltage drifts.

Low pass filter

Low pass filters attenuate high frequencies, and are therefore useful for removing high frequency movement (muscular) artefacts. Low-pass filters have been shown to smear out

ERP waveforms, and thus low-pass filtered ERPs have been found to start earlier and end later than unfiltered ERPs. However, when a high enough cut-off value such as 100 Hz is used, the filter has little effect on the ERP waveform (Luck, 2005). Therefore a low-pass cut-off value of 100 Hz was applied to my data to remove high frequency muscle artefacts.

Notch filter

Notch (band-stop) filters attenuate a narrow frequency band and are used to remove noise in the data due to electrical devices (which result in a 50 Hz artefact in the data). Although Luck (2005) suggests a high-pass filter with a 30 Hz cut off is a good alternative to notch filtering data (to avoid signal distortion from notch filtering), notch filters are useful when high frequencies (in the gamma range) are of interest for analyses. A notch filter was applied to my data so that the higher frequency data was retained, as we were interested in analysing data within the 55-90 Hz gamma range (discussed in chapter 5).

For each participant, the continuous EEG data file was loaded into the MATLAB environment (The MathWorks Inc., Natick, MA, 2012) using EEGLAB (Delorme & Makeig, 2004), and filters were applied using ERPLAB toolbox filters (Lopez-Calderon & Luck, 2014). Filtering was implemented prior to epoching the data (see section 4.2.3), as filtering continuous data prevents signal distortion due to filtering artefacts at epoch boundaries (Delorme & Makeig, 2004). The EEG data files were DC (direct current) recordings (no filters were applied to the data during recording). The application of a high-pass filter to DC recordings can add large distortions at the beginning and end of the signals (edge artefacts), therefore the ERPLAB function for removing this DC offset (subtraction of the mean voltage of the whole waveform from each data point) was implemented prior to filtering, as strongly recommended by Lopez-Calderon and Luck (2014).

Each of the filters used (Figure 4.2.) were applied to all 128 channels. Firstly, a band-pass filter (high and low pass filter) was run using the ERPLAB IIR (infinite impulse response) Butterworth filter (Lopez-Calderon & Luck, 2014), which is a zero phase shift non-causal filter (to prevent phase shift the filter is applied in both the forward and reverse direction). Cut-off values for this band-stop filter were 0.1-100 Hz. Subsequently, a stop-band Parks McClellan notch filter (Lopez-Calderon & Luck, 2014) was applied to the data using an attenuation value of 50 Hz. For further details regarding the filtering parameters used see Figure 4.2.

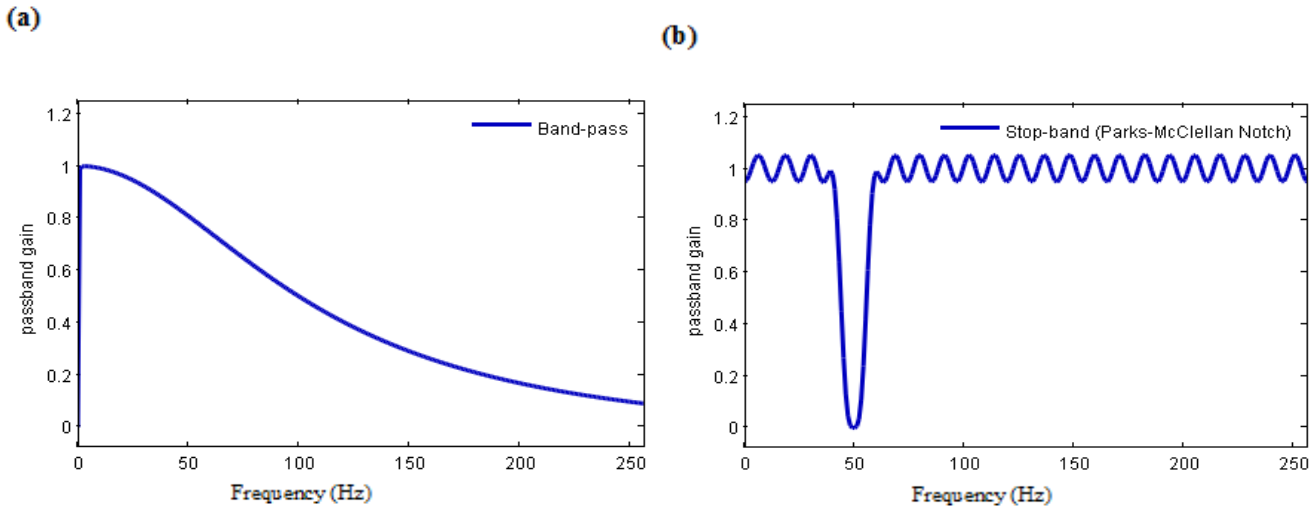


Figure 4.2. Filter frequency response graphs showing the frequencies attenuated by the filters applied to each participant's data (across all channels). **(a) IIR Butterworth filter** (non-causal), cut-off values: 0.1-100 Hz. Half-amplitude cut off (frequency at which the amplitude is attenuated by 50 %, equal to 6 dB attenuation): 100 Hz, filter order: 2. **(b) Parks-McClellan Notch filter** 50 Hz attenuation, filter order: 180.

4.2.2 Trigger coding

In the raw EEG recordings the ANT triggers (marking the onset of task stimuli and participant responses in the EEG data) were coded as numerical values ranging from 1-248; each corresponding to a unique combination of stimuli onset (cue and target) and participant response (correct, incorrect, missed). In order to convert these trigger values into useful labels for EEG analyses, I wrote a script to re-code the triggers so that they were compatible with ERPLAB functions, enabling data bins containing triggers with the same label to be grouped

together for subsequent analyses. Two scripts were written; one to define and extract bins containing cue triggers (bin labels: no cue, neutral, spatial), the other was designed to define and extract bins containing target triggers (bin labels: congruent, incongruent). Each script was written to extract only those cue and target triggers that were followed by a correct participant response for that trial (following target onset).

Triggers from trials in which the participant's reaction time was < 400 ms were coded separately (to other correct response triggers) and excluded from subsequent analyses. Such fast responses were judged to be 'automatic' responses to a stimulus onset as opposed to 'real' deliberated responses; the ANT requires a degree of conflict resolution (following the target presentation), consequently cognitive processing time is longer than that of a simple reaction time task. A reaction time of < 400 ms was deemed an appropriate cut-off point based on the available ANT literature; whilst young healthy individuals have demonstrated reaction times around approximately 400 ms (Fan et al., 2002), healthy elderly individuals tend to have slower reaction times (approx. 600-800 ms according to stimulus) (Deiber et al., 2013), and dementia patients have demonstrated reaction times between 600-1500 ms (Fernandez-Duque & Black, 2006; Fuentes et al., 2010). Furthermore, the behavioural data for our participant cohort (chapter 3) showed that the mean reaction time (for each task condition) was much greater than 400 ms for both the dementia groups and the age-matched controls (chapter 3, section 3.5).

4.2.3 Epoching the data

A crucial pre-processing step in event-related EEG analyses is the extraction of epochs, i.e. data segments time-locked to the onset of task stimuli, from the continuous EEG data. Using the scripts described in section 4.2.2., epochs time-locked to cue and target onset were created. Due to the variable cue to target onset latency (stimulus onset asynchrony, SOA), details of which are given in chapter 2 (section 2.5), it was necessary to extract cue and target epochs separately and save them in separate files. All epochs were created using boundaries of -600 ms (600 ms prior to cue/target onset) to 1500 ms (1500 ms post cue/target onset). These time intervals were chosen after careful consideration regarding the variability of the time lapse between cue and target onset, as well as the variable inter-trial interval time

(for details regarding the range of intervals of the ANT please refer to chapter 2, section 2.5). The majority of participants completed 8 runs of the ANT (each comprising 36 trials), therefore the maximum number of epochs (if all responses were correct) was 288; 96 for each cue condition (no cue, neutral, spatial), and 144 for each target condition (congruent, incongruent). All epochs were plotted and visually inspected to check for participant response triggers from the previous trial (in the 600 ms prior to stimulus onset), those epochs containing such triggers were removed from the data file.

4.2.4 Rejection of artefacts using visual inspection

It is crucial that artefacts are rejected during pre-processing of EEG signals as noise in the data can lead to invalid inferences being drawn when interpreting results. Common EEG artefacts include eye blinks and eye saccades (stereotyped artefacts), and non-stereotyped artefacts such as movement artefacts (primarily due to head and jaw movements), and shifts in voltage due to skin potentials and noisy channels. Artefacts can be identified by their characteristic waveforms (refer to Figure 4.3). The epoched data was carefully inspected visually in order to identify and manually reject epochs containing non-stereotyped artefacts. When artefacts were present in a trial the data for the whole trial was rejected, so for example when an artefactual cue epoch was rejected the corresponding target epoch for that trial was rejected, and vice versa. Visually inspecting the data was particularly useful for identifying and removing sporadic large amplitude, high frequency muscle artefacts (see Figure 4.3) which were present in many of the participants' recordings, particularly DLB patients. Numerous algorithms have been developed in an attempt to automate the detection and rejection of non-stereotyped artefacts, however after testing the efficiency of several algorithms (incorporated into the EEGLAB and ERPLAB toolboxes) it was apparent that manual rejection was the most effective technique for our data. Eye blink and eye movement artefacts were not removed manually as they tended to be consistently present throughout the EEG recordings (across all epochs); these stereotyped artefacts were removed using Independent Component Analysis (ICA) (see section 4.2.6).

For each participant group (controls, AD, DLB) the number of epochs used in the analyses (following epoch rejection) was comparable; for each task condition (cue and target)

there was no significant difference between the groups in terms of the average number of epochs used in the analyses.

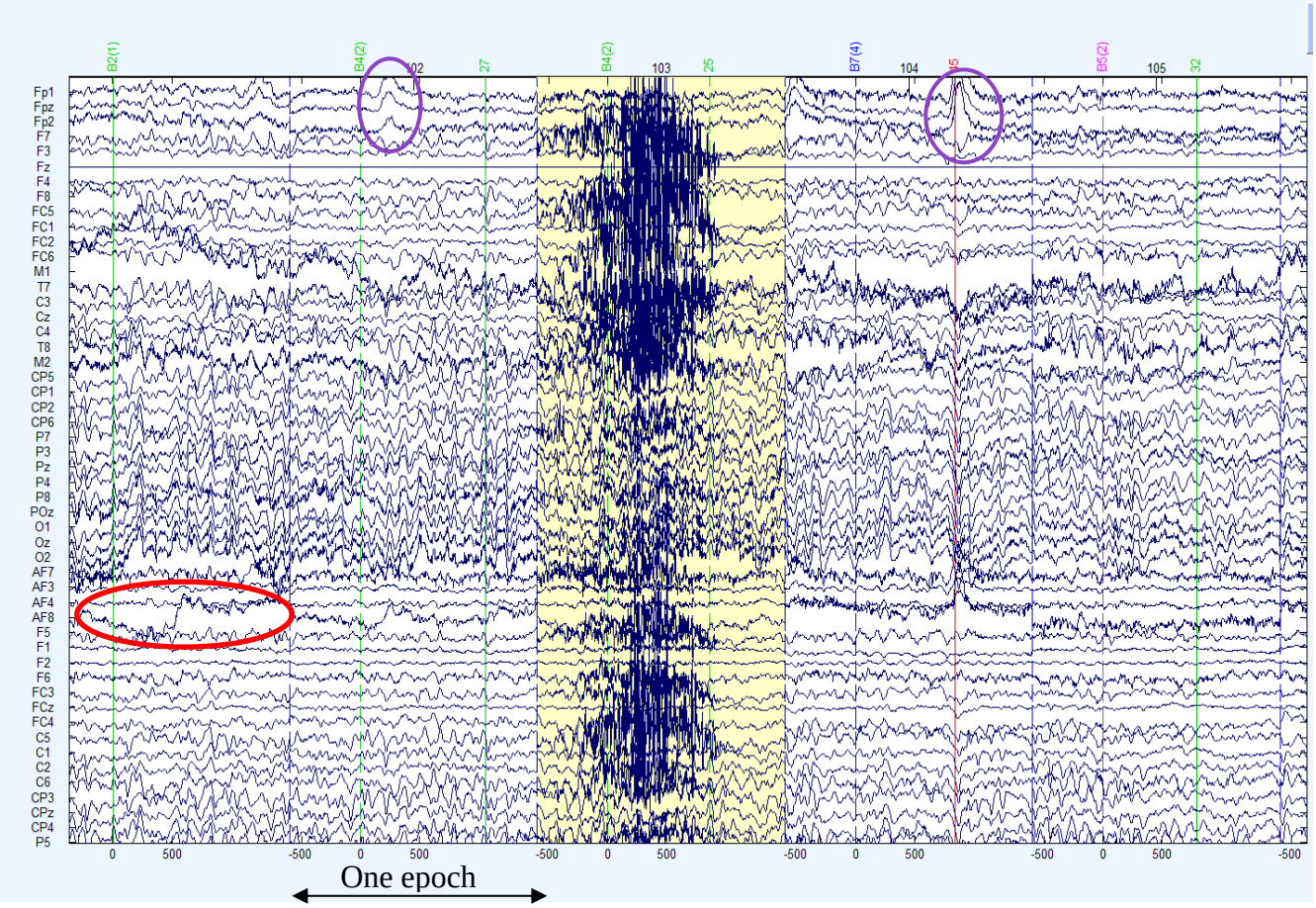


Figure 4.3. Plot depicting data epochs (in the time domain) in which artefacts are present. The epoch highlighted in yellow is an example of an epoch which would be rejected due to the presence of muscle artefact (high amplitude activity, usually evident across all channels). The voltage deflections encircled in purple are characteristic of eye blink activity (usually in the frontal electrodes), whilst the activity encircled in red is indicative of a shift in voltage due to an eye saccade. Note the epochs containing eye blink and eye saccade activity would not be rejected, this activity would be removed from the data using ICA (see section 4.2.6).

4.2.5 Identifying bad channels

During EEG recordings electrodes can become 'noisy' for a number of reasons e.g. head movements or the participant touching the cap which can result in electrodes losing

contact with the scalp, whilst skin potentials (sweating) can lead to voltage drifts. In order to identify bad channels, the EEGLAB automatic channel rejection function was applied to the data; kurtosis statistics were computed for each channel using a z score threshold of 5 (Delorme & Makeig, 2004). The data for each channel was visually inspected and this was used in conjunction with the automatic channel rejection function to ensure that all noisy channels were identified. The bad channels were noted and excluded from subsequent ICA analyses (section 4.2.6), as noisy channels can result in poor ICA decompositions (Ullsperger & Debener, 2010). These bad channels were then interpolated after ICA (see section 4.2.7 for interpolation details). When channels were noisy in single epochs only, as in Figure 4.4, the epoch was rejected instead of interpolating the channel.

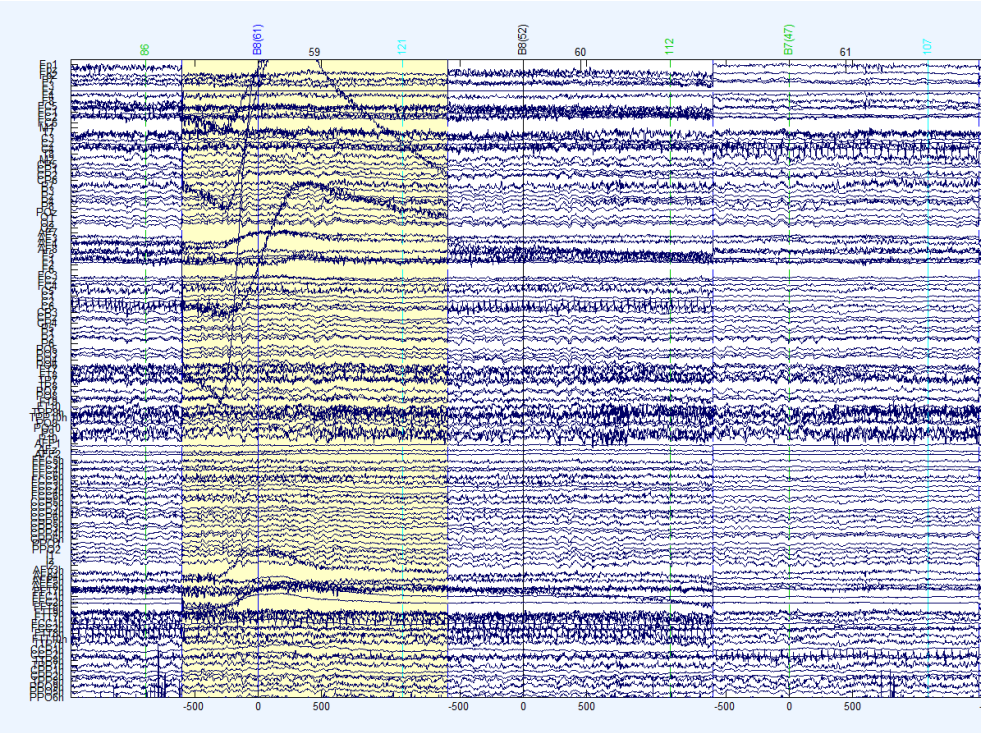


Figure 4.4. The epoch highlighted in yellow depicts channels exhibiting voltage drift in a single epoch only (as opposed to being consistently noisy across multiple epochs). In this case, the epoch would be rejected instead of interpolating the channels.

4.2.6 Independent component analysis (ICA)

Independent component analysis (ICA) is a computational linear decomposition technique and in signal processing it is used to separate multivariate signals into underlying source signals (components) (Hyvarinen, 2001; Jung et al., 2000; Makeig et al., 1997). ICA is a 'blind source separation' method (Bell & Sejnowski, 1995) as the analysis is conducted without any information regarding the number and spatial distribution of the source signals (Jung et al., 2000).

ICA has become a widely used technique in the pre-processing of EEG data. It is used to separate out the cortical activity and artefact components enabling signal sources to be identified which may not be identifiable from the raw recorded signal (Ullsperger & Debener, 2010). High-density EEG data can be modelled as a two dimensional matrix (X) comprising time points (rows) multiplied by the number of channels (columns). When ICA is applied to EEG data the output of ICA (W) is the square matrix of the size of the number of channels. The time courses of W, the independent components, can be modelled as follows (Ullsperger & Debener, 2010);

$$\mathbf{A = WX}$$

A= independent component time courses

W= square weight matrix

X= raw EEG data

The raw EEG data is reconstructed by multiplying **A** with the inverse of **W** ($\mathbf{W^{-1}}$), the mixing matrix:

$$\mathbf{X = AW^{-1}}$$

A - contains the time course of the independent components, whilst $\mathbf{W^{-1}}$ contains the spatial (topographical) information of the components (the spatial weights which apply to all of the time points equally).

Given that ICA identifies components which are maximally independent in the time domain, the technique is particularly useful for extracting (and removing) stereotyped artefacts from the mixed signal which are not phase-locked to each other (Delorme & Makeig, 2004). Therefore ICA is particularly useful for removing eye blink and eye movement artefacts which are intermittently present throughout EEG recordings.

Assumptions of ICA

There are a number of theoretical assumptions, listed below, which must be met in order for ICA to be effective. The steps which were taken to ensure that the assumptions inherent to ICA were met (as far as possible) for my EEG data are discussed below:

1) Non-Gaussian distribution

It is assumed that the distribution of the activations for the EEG sources are not perfectly Gaussian (Delorme & Makeig, 2004). Whilst EEG signals tend to exhibit fairly Gaussian distributions, it is acknowledged that it is difficult to determine the extent to which EEG data comprises non-Gaussian sources. However Ullsperger and Debener (2010) suggest that this assumption of non-Gaussian distribution is reasonable given the quality of many ICA decompositions.

2) Spatial stationarity

It is assumed that the data sources are stationary, and in the context of EEG recordings it is assumed that the spatial relationship between sources and channels is constant. This assumption is violated if there is drift in channel signals, for example if the cap moves or the participant moves (resulting in channel dislocation). For our data all bad channels were identified prior to ICA (and excluded from the analysis), and therefore it is reasonable to state that appropriate measures were taken in an attempt to fulfil the spatial stationarity assumption.

3) More signals than sources

For an effective ICA decomposition it is necessary for the number of channels to exceed the number of signal sources. Given that we used a high density cap (128 channels) this assumption is less likely to be violated than if we had used fewer channels during the recordings. Non stationary activity (e.g. channel drift) was also removed from the data prior to ICA which reduced the number of non-cortical (artefactual) sources.

4) Linear mixing

For ICA to be effective, it is assumed that all source signals add linearly and instantaneously (resulting in the recorded data being the linear sum of the source signals). This assumption is usually met for EEG recordings due to summed volume conduction at the scalp (Ullsperger & Debener, 2010). No channel activity should be a linear mixture of the activity of other channels, however it is possible that this can occur for average-referenced data (Delorme, 2004). Therefore ICA was conducted prior to channel interpolation (section 4.2.7) and average-referencing (see section 4.2.8).

5) Statistical independence

It is assumed that the signal sources are statistically independent. This assumption may not be fully met when ICA is applied to EEG data due to the likelihood of a degree of temporal coupling of cortical sources. However Ullsperger and Debener (2010) have shown that partial independence of sources (whereby sources exhibit a degree of temporal independence) is sufficient for effective ICA decomposition of EEG data.

4.2.6.1 FastICA algorithm

As the popularity of ICA for EEG signal decomposition has grown, numerous different ICA algorithms have been developed. Whilst it is difficult to evaluate the extent to which each of the algorithms meet the ICA assumptions, the most commonly used algorithms

seek to detect maximally independent components and have been found to detect broadly comparable components (Delorme & Makeig, 2004; Klemm et al., 2009). Following pilot analyses to investigate the efficiency of several commonly used ICA algorithms (including JADE, FastICA, and Informax), FastICA (Hyvarinen, 1999; Hyvarinen & Oja, 2000), which has been shown to be highly effective at separating EEG components (Klemm et al., 2009), was judged to be the most efficient algorithm for use with our high-density EEG data (as discussed below).

The FastICA algorithm uses a fixed point iteration method, the deflation approach was selected which involves computing components successively one by one (Tichavsky et al., 2006), as opposed to computing all independent components at once as done by several other popular gradient-descent ICA algorithms. It is a well-established computationally efficient algorithm, and when it was applied to our data I found that it returned high quality ICA decompositions (the decompositions were comparable to those yielded when using other algorithms) but was much faster at converging to a solution than other algorithms, which was an important factor given our large datasets. The algorithm includes a pre-processing step in which the data is 'centred', the mean is subtracted from the data, and subsequently 'whitened', whereby the data is linearly transformed and the new components are uncorrelated; thus enabling fast convergence to a solution. The number of independent components returned by the ICA decomposition is equal to the number of electrodes (128, or less if bad channels were excluded prior to ICA).

It is recommended that a 1 Hz high-pass filter is used for ICA as low frequency activity is often spatially unstable and can therefore violate the stationarity assumption leading to poor quality decompositions (Ullsperger & Debener, 2010). However, as such a high cut-off (1Hz) value is known to reduce ERP amplitude (Luck, 2005) a cut-off of 0.1Hz was used for our data (discussed in section 4.2.1). To overcome this problem, it has been suggested ICA should be applied to 1Hz filtered data and the results (ICA weights) then applied to the same participant's data which is filtered using a lower cut off value (i.e. 0.1 Hz), thus enabling the identification of low frequency components (e.g. eye blinks) whilst retaining the low frequencies in the signal necessary to obtain the expected ERP amplitudes. In summary, the FastICA algorithm was applied to 1-100 Hz band-pass (and notch) filtered

epoched data (the same epochs were rejected as the 0.1 Hz filtered data, and the same bad channels excluded prior to ICA). These data epochs (1 Hz filtered) for the cue and target conditions were concatenated, and ICA was applied to all of the epochs (as opposed to running separate ICA decompositions for the cue and target conditions). The independent components were then applied to the 0.1-100 Hz, notch filtered data and the artefact components rejected. This approach was advantageous in terms of computational processing time, and it also ensured that the same pre-processing steps were conducted for each task condition; in particular the same artefact components were rejected for the cue and target task conditions.

Identifying and removing artefactual components

The purpose of applying ICA to our data was to remove only those components which were clearly identifiable as artefacts, primarily eye blink and eye movement artefacts (see Figure 4.5). When continuous movement (muscle) artefact was present throughout the EEG data, components which clearly represented this artefact were also removed. Eye blink artefacts tend to have a stable spatial distribution and consequently eye blink components are often easily identifiable (see Figure 4.6). Eye blinks are often represented by a single component, although it is possible for more than one component to represent eye blink activity if their time courses differ slightly.

Independent components representing artefacts can be identified by examining several component properties; the component activity in the time domain, the spatial distribution of the activity (topography), and power of the activity at each frequency. Topographical plots are particularly useful for differentiating artefactual and cortical components (Figure 4.5). All of the components were visually inspected by me in order to identify and reject the appropriate components. Whilst more objective methods have been developed to identify artefact components, many of these methods have not been validated (in terms of efficiency at separating cortical and non-cortical activity), therefore visual inspection is still recommended as the preferable method for component identification (Ullsperger & Debener, 2010).

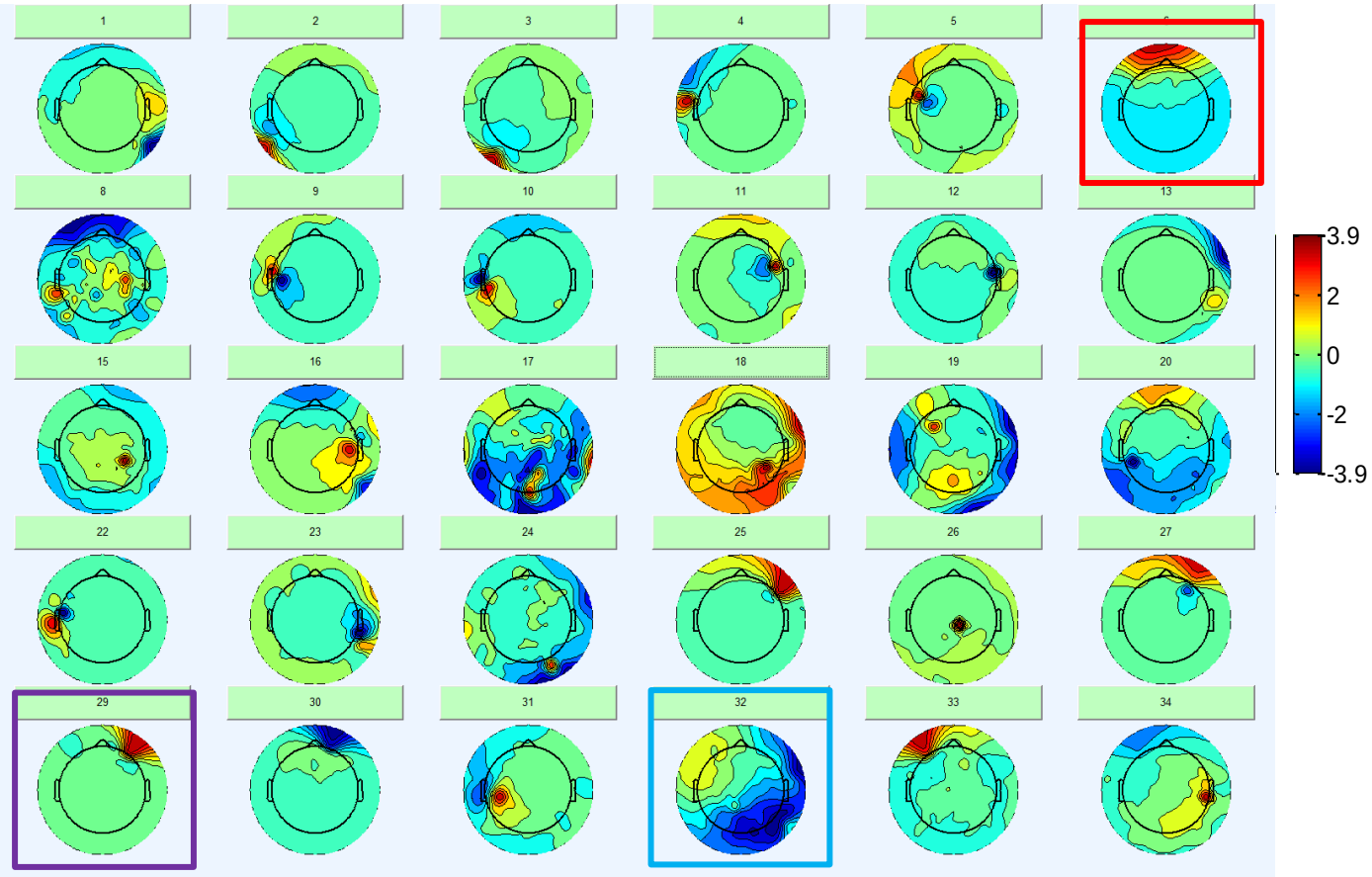


Figure 4.5. Example topography plots of independent components depicting the spatial distribution of the component activity, the scale shows the relative amplitude (μV) of the activity. Components representing cortical activity tend to show dipolar activations, whereas artefact components tend to show non-dipolar activity focused over a narrow area (as opposed to more diffuse activity frequently observed in components representing cortical activity). The topography plot enclosed in the red square depicts the characteristic spatial distribution of eye blink activity (frontal activity). The component enclosed in the purple square is typical of a lateral eye movement (focused frontal activity, not dipolar). The component in the blue square shows widespread cortical activity (such a spatial distribution is characteristic of posterior alpha activity).

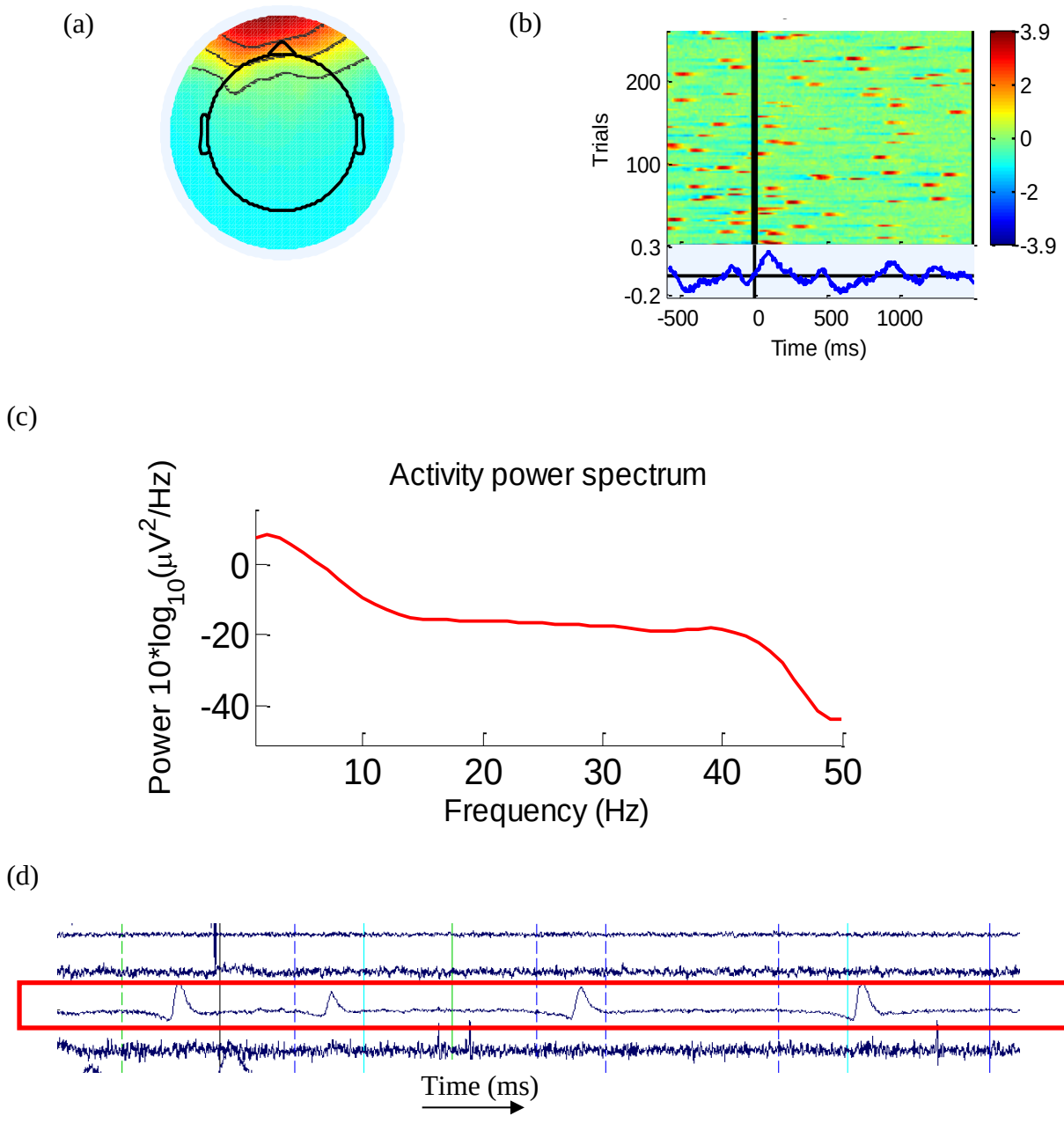


Figure 4.6. An independent component representing an eye-blink artefact

(a) Topography plot shows frontal activity (non-dipolar) **(b)** The ERP (event-related potential) activity (shown by the blue line, 0 ms represents stimulus onset) does not show a clear peak as the component activity is not synchronised to the stimulus onset. The activity is evident intermittently across trials (shown on the Y axis), the scale bar represents relative amplitude (μV). **(c)** The power spectrum, depicting the average power change with respect to baseline, shows that the power is highest at low frequencies (and there is an absence of a clear peak in the alpha and beta range which is often present for cortical components). **(d)** Component activity plotted in the time domain (encapsulated in the red rectangle) that is characteristic of eye blinks; regular deflections in the signal not synchronised with stimulus onset (although synchronisation of eye blinks with a stimulus can occur).

4.2.7 Channel interpolation

Channel interpolation involves using the signal data from the channels surrounding a bad channel to create an estimate of the activity of this channel (in effect replacing the 'bad' data). The channels marked as bad prior to ICA (section 4.2.5) were interpolated using the EEGLAB spherical spline interpolation function (Delorme, 2004). Spherical splines are especially useful for interpolating EEG channels as they assume spherical head geometry and account for the curvature of the scalp (Perrin et al., 1989). Whilst it is possible to perform channel interpolation either before or after average referencing (section 4.2.8), it is recommended that interpolation is performed prior to average referencing as interpolated channels can be used to improve the estimate of the average reference (Ferree, 2006). No more than 10 % of channels were interpolated for each participant's data (a cut-off widely accepted and implemented by the EEG community). However, for the majority of participants the number of interpolated channels was much lower than this; on average it was approximately 5 % of channels.

4.2.8 Average referencing

All EEG data is recorded using a reference; an arbitrarily chosen point which is assigned a value of zero to which all of the voltage potentials are measured. Re-referencing EEG data is a common pre-processing step which is implemented to remove any effect of the reference (assigned during recording) during subsequent analyses. Whilst there are many different possible ways to re-reference the data, average referencing, the average potential of all of the channel signals, is one of the most popular re-referencing methods. Average referencing is particularly useful for high-density EEG data as average reference estimates tend to improve as the number of channels covering the scalp increases (Bertrand et al., 1985; Dien, 1998). For each participant, the EEG data were re-referenced from Fz (assigned during recording-see chapter 2) to the average reference (of all channels).

4.2.9 Defining regions of interest

For the purposes of the time-frequency analyses (see section 4.3.2) regions of interest were created by averaging the signals of groups of channels. Seven regions of interest were created; frontal (divided in left and right hemisphere), central (left and right hemisphere), parietal (left and right hemisphere), and occipital; see Figure 4.7 for details of the channels which were averaged for each region. Averaging channels in order to define areas of interest is frequently implemented prior to conducting EEG analyses as a means to aid interpretation of the results. In event-related EEG research, an increasingly popular alternative to this region of interest approach is source localisation; the use of mathematical models to determine the origin of the activity recorded at the scalp. Event-related source localisation is a complex process, and whilst currently available source localisation techniques are able to provide an estimate of the distribution of the source, it is not possible to quantify the extent to which these localisation estimates are accurate (Luck, 2005). Therefore for the purposes of the present work it was decided that the analyses would be conducted based on the activity over well-defined regions, as opposed to attempting to determine the sources of the activity.

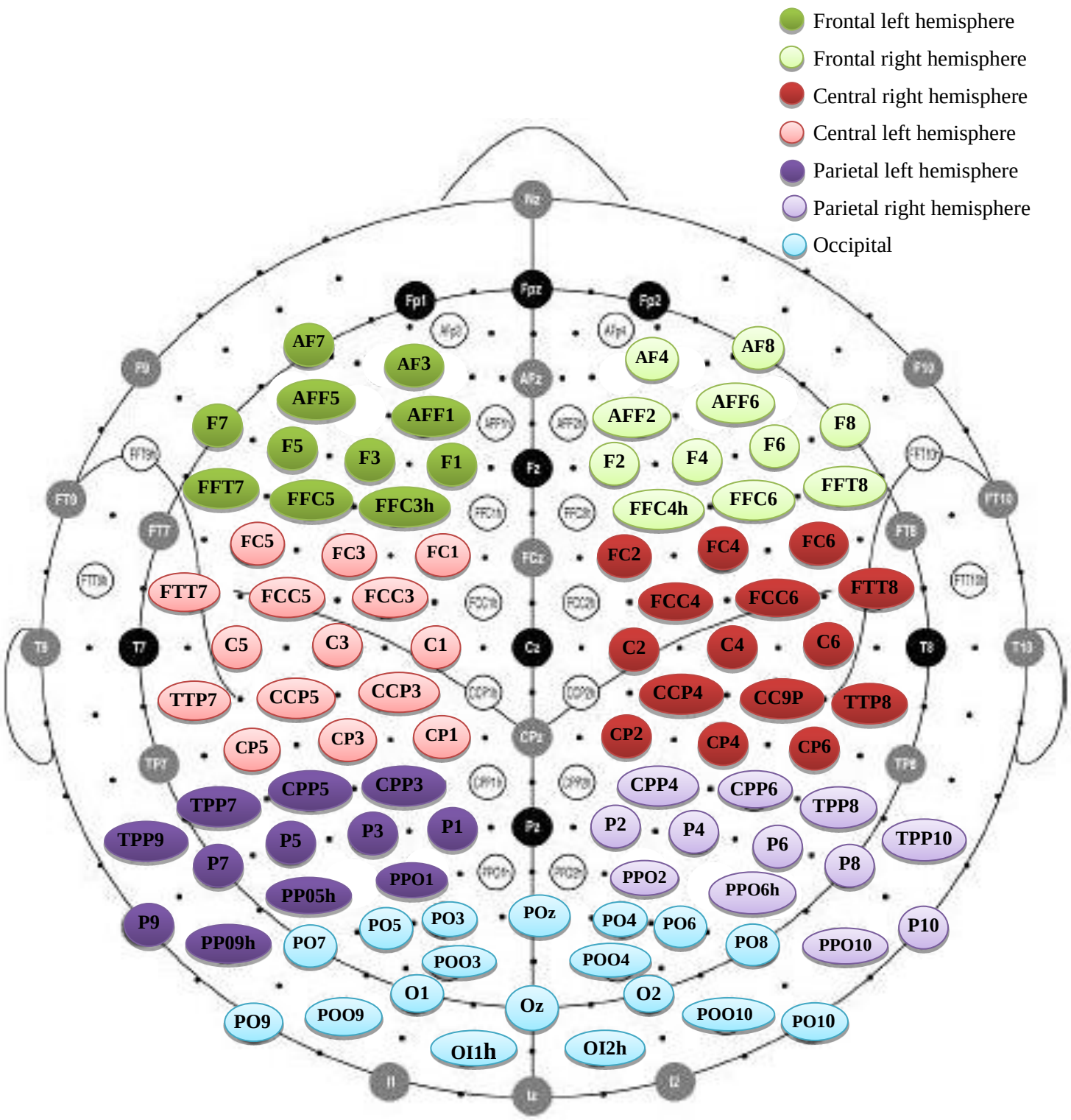


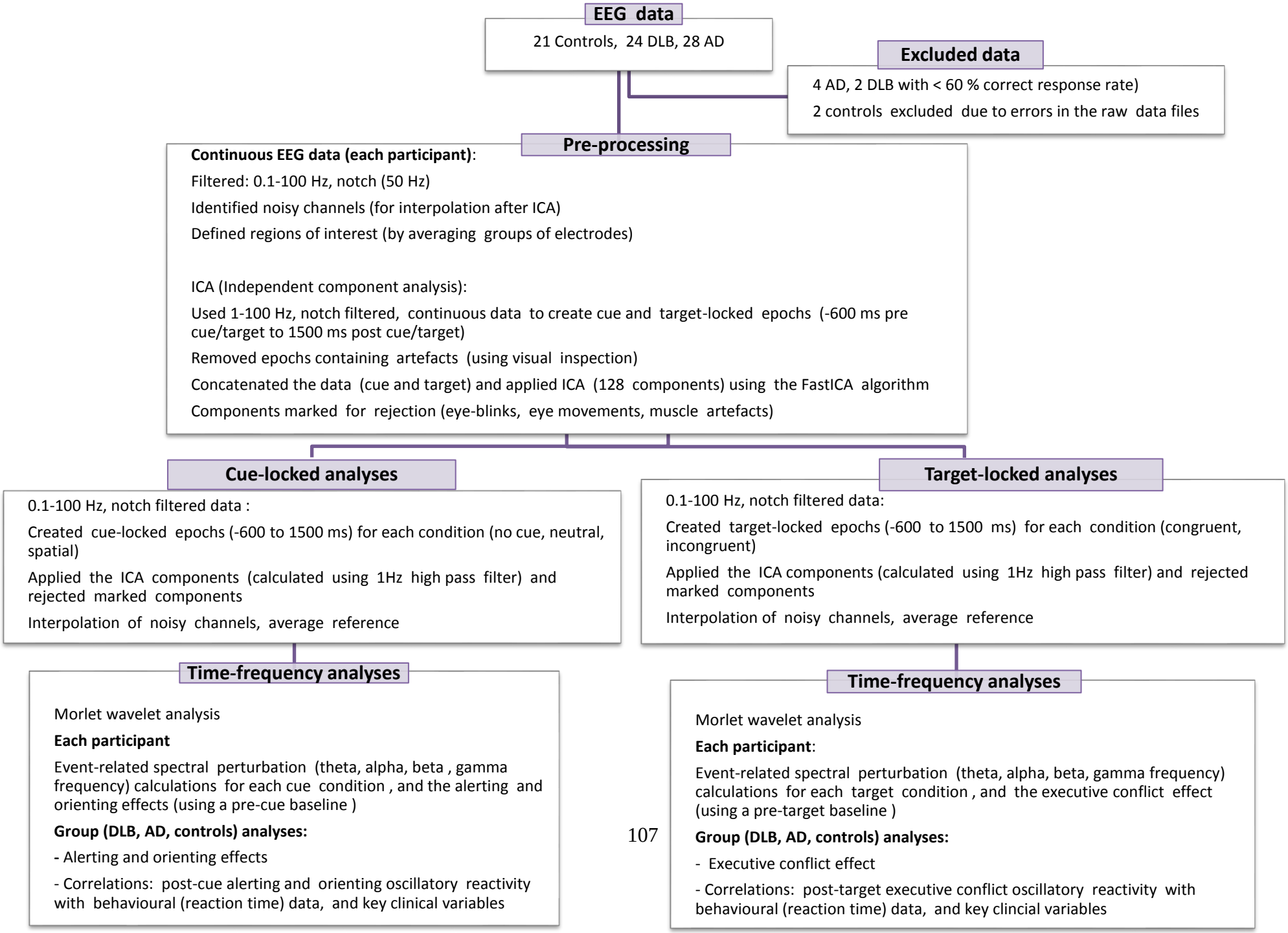
Figure 4.7. The head model illustrates the electrodes, depicted in accordance with the 10-5 placement system (Oostenveld & Praamstra, 2001), which were used to define each region of interest. The different coloured electrodes indicate the electrodes which were used to define each region of interest (shown in the figure legend). To minimise the presence of artefacts in the averaged signals, the more peripheral electrodes were not included in the averaging process; signals of peripheral frontal electrodes are usually noisy due to eye blinks and movements, whilst the peripheral electrodes located over the central/temporal areas tend to be affected by movement artefacts (primarily due to jaw movements).

4.3 EEG analyses pipeline

An overview of the EEG analyses pipeline is given in section 4.3.1. As indicated in section 4.3.1, the EEG data from participants who demonstrated poor task performance was excluded prior to pre-processing of the data. As with the behavioural analyses (chapter 3), participants with a response rate < 60 %, and those with a response rate > 60 % but < 60 % of responses correct, were excluded. It was necessary to exclude individuals with poor task performance to ensure that there were a sufficient number of correct response epochs from each participant for averaging during subsequent analyses (section 4.3.1). Whilst a 60 % cut-off rate is fairly low, it ensured that the DLB data was representative of the DLB cohort; using a higher cut-off rate would have likely resulted in the more impaired individuals with DLB (those more likely to experience greater severity of cognitive fluctuations) being excluded from subsequent analyses. Given that a lower percentage of correct response trials (i.e. 50 %) is likely to be indicative of individuals responding by chance alone, a 60 % cut-off rate was deemed to be appropriate.

Upon completion of the pre-processing of the EEG data, participants' data were analysed using time-frequency analyses in order to investigate the spectral characteristics of the data (section 4.3.3).This approach, which involved investigating the data in both the time and frequency domains, ensured that all potentially useful information was extracted from the EEG data, therefore facilitating the characterisation of the aberrant neurophysiology underlying the attentional network deficits exhibited by the dementia patients (discussed in Chapter 3).

As discussed briefly in chapter 2, due to the greater severity of aberrant motor activity in the PDD patients relative to the DLB patients, the PDD patients' EEG data tended to contain substantial movement artefacts. Removal of such artefacts from the data would require extensive pre-processing (more so than the DLB patients), it was therefore decided that the DLB and PDD patients should be treated as separate groups for the EEG analyses. For the purposes of this thesis, only the DLB patients' data was analysed due to the complex and time-consuming nature of the analyses conducted. For the demographics of the participant cohort used in the time-frequency analyses please see chapter 5 (section 5.3).


EEG data
21 Controls, 24 DLB, 28 AD
Excluded data
4 AD, 2 DLB with < 60 % correct response rate)
2 controls excluded due to errors in the raw data files
Pre-processing
Continuous EEG data (each participant):
Filtered: 0.1-100 Hz, notch (50 Hz)
Identified noisy channels (for interpolation after ICA)
Defined regions of interest (by averaging groups of electrodes)
ICA (Independent component analysis):
Used 1-100 Hz, notch filtered, continuous data to create cue and target-locked epochs (-600 ms pre cue/target to 1500 ms post cue/target)
Removed epochs containing artefacts (using visual inspection)
Concatenated the data (cue and target) and applied ICA (128 components) using the FastICA algorithm
Components marked for rejection (eye-blinks, eye movements, muscle artefacts)
Cue-locked analyses
0.1-100 Hz, notch filtered data :
Created cue-locked epochs (-600 to 1500 ms) for each condition (no cue, neutral, spatial)
Applied the ICA components (calculated using 1Hz high pass filter) and rejected marked components
Interpolation of noisy channels, average reference
Target-locked analyses
0.1-100 Hz, notch filtered data:
Created target-locked epochs (-600 to 1500 ms) for each condition (congruent, incongruent)
Applied the ICA components (calculated using 1Hz high pass filter) and rejected marked components
Interpolation of noisy channels, average reference
Time-frequency analyses
Morlet wavelet analysis
Each participant
Event-related spectral perturbation (theta, alpha, beta , gamma frequency) calculations for each cue condition , and the alerting and orienting effects (using a pre-cue baseline)
Group (DLB, AD, controls) analyses:
- Alerting and orienting effects
- Correlations: post-cue alerting and orienting oscillatory reactivity with behavioural (reaction time) data, and key clinical variables
Time-frequency analyses
Morlet wavelet analysis
Each participant:
Event-related spectral perturbation (theta, alpha, beta, gamma frequency) calculations for each target condition , and the executive conflict effect (using a pre-target baseline)
Group (DLB, AD, controls) analyses:
- Executive conflict effect
- Correlations: post-target executive conflict oscillatory reactivity with behavioural (reaction time) data, and key clincial variables

4.3.2 Time-frequency analyses

As discussed in chapter 1, the temporal and spatial characteristics of event-related oscillations can be analysed concurrently by means of time-frequency analyses. Time-frequency analysis approaches decompose event-related oscillations into phase and magnitude information for each frequency (or specified frequency band) at each time point, therefore enabling the spectral decomposition over time (with respect to stimulus onset) to be analysed (Roach & Mathalon, 2008).

Numerous mathematical approaches have been developed for the purpose of conducting time-frequency analyses of EEG signals. For the present study I chose a wavelet analysis approach for our data (described in detail in Chapter 5). Wavelet analyses were conducted to characterise the event-related spectral perturbation of post-cue and post-target oscillatory activity within the frequency range 4-90 Hz.

4.4 Discussion

Whilst there is a degree of subjectivity associated with the pre-processing (and analyses) of EEG data, the methods discussed throughout this chapter were devised and implemented after careful evaluation to determine the most appropriate techniques for our data. Visual inspection, which is inherently subjective, was used to identify non-stereotyped artefacts in the data, as well as to identify artefactual ICA components, as it was judged to be a more effective method than automated techniques which were applied to our data. Whilst numerous algorithms have been developed to aid the identification of non-stereotyped artefacts in EEG data, many have yet to be validated; consequently visual inspection of EEG data is still common procedure to identify such artefacts, as it often results in superior data cleaning relative to more automated techniques (Luck, 2005; van Diessen et al., 2014). All of same pre-processing steps were applied to each participant's data, and all of the pre-processing was implemented by one individual (myself), and therefore there was consistency across the participants' data with respect to the judgements made regarding visual inspection of the data.

MATLAB toolbox functions from EEGLAB and ERPLAB were used throughout the pre-processing of the EEG. These toolboxes have been developed specifically for EEG analyses and are well-established and widely used within the EEG community. Whilst it is true that there is a vast degree of heterogeneity in the methods used to pre-process EEG data, the use of such toolboxes goes some way to standardising the analyses of our data.

For all EEG analyses, a judgement must be made regarding the extent to which the original signals should be modified in order to increase the signal-to-noise ratio; this issue was particularly pertinent when analysing the dementia patients' data which tended to contain an extensive amount of noise. Attempting to remove all noise from the data was not appropriate; independent components in which artefacts appeared to be mixed with cortical activity were not removed, as this activity could potentially contribute to the aberrant neurophysiology underlying the cognitive phenotype of the dementia patients. However, the effects of any noise remaining in the data were minimised by the averaging process conducted during the subsequent time-frequency analyses (Chapter 5), and a similar number of epochs were used for each group (dementia patients and controls) during the averaging process.

Chapter 5 . Oscillatory reactivity of the attentional networks in DLB: methodology

Following the pre-processing of the EEG data (described in chapter 4), the data were used to conduct a comprehensive time-frequency analysis. In this chapter I explain in detail the time-frequency analysis methodology, and provide an overview of the participant cohort used in the analyses. The results of these time-frequency analyses which were conducted for each task condition (cue and target) are presented in chapter 6, and the results of each of the attentional network analyses are described in chapter 7. Finally, I discuss all of the time-frequency analyses results (as presented in chapters 6 and 7) in chapter 8.

5.1 Introduction

The study of attention from an electrophysiological perspective traditionally involved the use of the event-related potential (ERP) technique; whilst this method is highly informative with respect to the timing of event-related EEG activity, it is limited in terms of the information which can be derived regarding complex brain dynamics (Grandchamp & Delorme, 2011). Over the last 20 years there has been an emergence of event-related spectral analysis techniques, frequently referred to as time-frequency analyses, which provide both time and frequency information regarding changes in oscillatory activity following a stimulus. Time-frequency analysis approaches decompose event-related oscillations into phase and magnitude information for each frequency (or specified frequency band) at each time point, therefore enabling the spectral decomposition over time (with respect to stimulus onset) to be analysed (Roach & Mathalon, 2008). The oscillatory activity calculated using time-frequency analyses is a measure of task-related synchronisation of neuronal populations; the extent to which event-related synchronisation (ERS) and event-related desynchronsiation (ERD) is evident is an indicator of the underlying neuronal processes associated with the task (Klimesch, 1999). Relative to ERP analyses, time-frequency analyses provide a more comprehensive analysis of event-related activity; the oscillatory reactivity evident at different frequencies provides an insight into various neuronal and cognitive processes occurring, and

thus may be more sensitive to pathophysiological processes than ERP analyses (Roach & Mathalon, 2008).

There is extensive literature regarding oscillatory correlates of visual attention; whilst there is a vast degree of heterogeneity in the attentional tasks and analysis methods used across studies, there is consensus regarding the role of oscillatory reactivity at various frequencies with regard to aspects of attentional processing. In particular, there is a substantial body of literature on alpha band reactivity (typically defined as 8-13 Hz) in the context of attention. Following the presentation of visual stimuli, alpha ERD (suppression of alpha power) has been shown in regions actively engaged in attending to the stimuli (Herrmann & Knight, 2001; Pfurtscheller & Lopes da Silva, 1999), whereas in regions not involved in processing task stimuli an increase in alpha activity has been observed, indicative of alpha ERD having a role in sensory gating of attention (Herrmann & Knight, 2001). Alpha ERD has also been found to be evident during tasks specfically designed to assess attentional function; a decrease in alpha activity has been shown following target presentation in a visual oddball paradigm (Klimesch et al., 1998), and has been associated with alerting following cueing stimuli prior to the onset of target stimuli (Babiloni et al., 2004). This alpha reactivity is generated by cortical neurons, yet thought to be driven by the thalamic structures (Herrmann & Knight, 2001; Steriade et al., 1990).

Comparable to alpha band reactivity, beta (14-30 Hz) ERD is associated with attending to visual stimuli; in attention tasks requiring a motor response, beta ERD following cueing stimuli (prior to target onset) has been found to be an oscillatory correlate of the selection and preparation of an appropriate motor response (Kaiser et al., 2001). During attentional tasks, in the post-cue interval (prior to a task based target onset) the extent to which both alpha and beta ERD is evident has been found to influence post-target oscillatory reactivity, and is therefore considered to be an indicator of the recruitment of attentional resources (Frey et al., 2015).

Fast cortical oscillatory gamma band activity (in the 30-100 Hz range) has also been associated with cognitive and attentional processing (Herrmann & Knight, 2001; Muller et al., 2000). Increased gamma band power has been observed over visual cortical areas during visual tasks requiring selective attention (Keil et al., 2001). In addition, attended visual

stimuli have been shown to elicit greater gamma synchronisation in the somatosensory cortices relative to unattended stimuli (Bauer et al., 2006), supporting the notion that gamma band synchronisation is a crucial neurophysiological mechanism in selective attentional processing (Jensen et al., 2007).

There is extensive literature on low frequency theta range (4-8 Hz) oscillatory activity in relation to memory function, particularly working memory (Klimesch, 1999), therefore consideration of theta reactivity in the context of attention is highly pertinent given the interdependence of working memory and attention (Baddeley, 1992; Missonnier et al., 2006a). Theta activity has been implicated in aspects of executive attention such as error monitoring (Luu et al., 2004), whilst spatial attention has been found to modulate oscillatory activity in the theta range (Frey et al., 2015). In a study which assessed young healthy individuals using a visual attention task (oddball detection task), Missonnier et al. (2006a) observed an increase in theta ERS in the initial 500 ms post-stimulus onset; this ERS had a widespread distribution (across all regions of interest), but was of greatest power in the frontal and central regions. The authors suggested that this theta ERS was an electrophysiological correlate of allocation of attention to target stimuli, and concluded that theta ERS plays a role in integrating visual information for further cognitive processing (Missonnier et al., 2006a).

Due to the extensive literature regarding oscillatory activity associated with attention, and the disparities between the studies in terms of methodologies and domains of attention investigated, it is difficult to draw valid inferences regarding the role of oscillatory activity at different frequencies in relation to various fractionated aspects of attention. The utility of the ANT, in terms of investigating electrophysiological correlates of attention, lies in the ability to evaluate three distinct attentional networks (alerting, orienting, executive conflict) in a single task. As all three networks have been validated and characterised, both in terms of associated functional structures and neurotransmitter systems (Fan et al., 2005), examination of the oscillatory reactivity associated with each of the networks has the potential to provide an insight into the neurophysiological mechanisms underlying the three fractionated elements of attention.

As discussed in chapter 1 (section 1.5.2), Fan et al. (2007) investigated the oscillatory activity (between 4-100 Hz) associated with each of the attentional networks by assessing a

cohort of 36 young healthy participants using the ANT. The alerting network was associated with desynchronisation (ERD) of theta, alpha, and beta activity between 200-450 ms post-stimulus. This desynchronisation was evident across the majority of sources of interest (derived from dipole source localisation); the authors suggested that this widespread ERD may indicate involvement of the thalamocortical system in regulating the alerting network. The orienting network was associated with gamma ERS at approximately 200 ms post-stimulus; this was predominantly evident in the fusiform gyrus and right superior parietal lobe sources, indicative of gamma ERS in these sources having an integral role in orienting of attention. For the executive conflict effect, Fan et al (2007) found that in the initial 400 ms post-stimulus there was ERS over a broad range of frequencies including the gamma band; this fits with the oscillatory activity associated with the anterior cingulate cortex, which has been found to be associated with action monitoring and is an integral structure of the executive conflict network (Fan et al., 2005).

Deiber et al. (2013) used a modified version of the ANT to investigate age related modulations in oscillatory activity (between 4-30 Hz); the cohort comprised 20 young and 28 healthy elderly individuals. Comparable to the Fan et al. (2007) study, there was an initial ERD in the alpha and beta ranges following the presentation of both the cue and target stimuli, however in addition there was also an early ERS in the theta range. In the no cue condition, posterior alpha ERD (prior to target onset) was attenuated in the elderly relative to the young group. Given that alpha ERD in posterior regions has been found to be associated with anticipatory attention for impending stimuli (Pfurtscheller & Lopes da Silva, 1999), the authors concluded that the elderly individuals engaged less anticipatory attentional resources than the younger individuals. Relative to the young group, the elderly group also showed reduced midparietal alpha ERD associated with the alerting effect, and decreased posterior alpha activation associated with the orienting and executive conflict effects. Deiber et al. (2013) suggested that there was an overall reduction in task-related alpha reactivity in the elderly individuals; in the young group oscillatory reactivity was most evident in the alpha band over posterior regions, whereas the predominant reactivity in the elderly group was in the beta band over the central regions.

The oscillatory reactivity of the attentional networks has yet to be investigated in individuals with dementia. In particular, examining the oscillatory reactivity of individuals with DLB (in the context of the attentional networks) has the potential to provide an insight into the pathophysiology underlying the significant attentional dysfunction exhibited by DLB patients.

5.1.1 Objective

The aim of the time-frequency analysis was to use the modified ANT to examine the oscillatory reactivity associated with the each task condition (cue and target), as well as each of the attentional networks, and deduce the extent to which this reactivity differed between the controls, AD group, and DLB group. Furthermore, for each of the attentional networks, associations between the oscillatory reactivity in the dementia groups and clinical measures of cognition and cognitive fluctuations were investigated. Associations between the oscillatory reactivity for each of the networks and the corresponding behavioural (reaction time) data were also examined.

5.1.2 Hypotheses

As described in chapter 1 (section 1.6.2), based on existing literature the following hypotheses were made regarding oscillatory reactivity in DLB:

- It was hypothesised that atypical neuronal synchrony, generated by the thalamocortical system, is a contributory factor underlying the attentional dysfunction exhibited by individuals with LBD. It was therefore predicted that the DLB group would show aberrant oscillatory reactivity following ANT stimuli presentation.
- It was hypothesised that atypical oscillatory reactivity is a contributory factor underlying cognitive fluctuations in LBD. As cognitive fluctuations are postulated to be associated with cholinergic system integrity, it was predicted that in the DLB group oscillatory reactivity associated with the orienting network (suggested to be regulated by the cholinergic system) would correlate with clinically assessed cognitive

fluctuations. In addition, given that alerting is the ability to maintain an alert state, it was hypothesised that the oscillatory reactivity associated with this network would correlate with cognitive fluctuation severity. In particular, as cognitive fluctuation severity in DLB has been found to be associated with slowing of posterior oscillatory activity, for these networks, it was predicted that low frequency reactivity over posterior regions would correlate with fluctuation severity.

5.2 Time-frequency analyses methods

The objective of my time-frequency analysis was to characterise the spectral perturbations in response to the task stimuli (cue and target), and I used a spectral estimation technique known as event-related spectral perturbation (ERSP) which is discussed in the following paragraphs. All time-frequency analyses were conducted using EEGLAB (Delorme & Makeig, 2004) custom spectral decomposition techniques (details of the analyses parameters are discussed in sections 5.2.2 and 5.2.3).

Event-related spectral perturbation (ERSP)

The ERSP technique, devised by (Makeig, 1993), was used to estimate the post-cue and post-target spectral alterations. The ERSP post-stimulus estimation approach involves computing both ERD and ERS across the frequency range of interest; the ERSP approach is thus an amalgamation of the ERD and ERS techniques (Delorme & Makeig, 2004). ERSP calculation involves computing power spectra over a sliding latency window for each stimulus-locked trial, and subsequently averaging across all of the trials (Delorme & Makeig, 2004). As a result, power values (perturbations relative to a pre-stimulus baseline interval) are generated for each frequency, at each time point relative to the time-locking event. The ERSP technique can be formalised as follows (Delorme & Makeig, 2004; Grandchamp & Delorme, 2011):

$$\mathrm{ERSP}(f,t) = \frac{1}{n}\sum_{k=1}^{\mathrm{n}} |F_K(f,t)|^2$$

n represents the total number of trials

$F_k(f, t)$ represents the spectral estimate for trial ***k*** at time point ***t*** and frequency ***f***

There are numerous approaches to calculate the spectral power estimates ($F_k(f, t)$) with differing advantages and disadvantages; for the presented analyses I decided to use the wavelet transform approach, and discuss reasons for this in section 5.2.1. There is also substantial heterogeneity with respect to the baseline correction techniques used for ERSP analyses, and I discuss the baseline correction parameters used in section 5.2.3.

5.2.1 Wavelets

There are a variety of windowing approaches which can be used to calculate the spectral estimates for EEG time-frequency analyses. Whilst an in depth discussion regarding the different windowing techniques is beyond the scope of this chapter, it is important to note that for all windowing techniques there is a trade-off between the frequency and temporal resolution. As a general rule, the larger the time window used to estimate the complex data for a given time point, the greater the frequency resolution but the poorer the temporal resolution (Roach & Mathalon, 2008).

Traditionally, one of the most commonly used windowing techniques for time-frequency analyses is the short-time Fourier transform (STFT); a windowed variant of the Fast Fourier Transform (FFT), whereby a Fourier transform is applied within a specified time window, and a sliding window (typically of fixed duration) is used to characterise the power of the EEG data over time across all frequencies of interest (Roach, 2008). The STFT approach is constrained by the use of a time window with fixed duration. Ideally, in order to optimise the time-frequency resolution trade-off, the length of the time window should be modified in accordance with the frequency to which it is applied. For optimal temporal resolution, shorter time windows are required for high frequency signals relative to low frequency signals.

One time-frequency approach whereby window size can be modified with respect to frequency (to optimise the temporal resolution at each frequency) is the Wavelet transform approach. Wavelets are wave-like oscillations (mathematical models of waveforms) which have a limited duration, are localised in both time and frequency space, and have an average value of zero (Roach, 2008). When a complex wavelet function is used, wavelet transforms yield the phase and amplitude of the signal for the specified frequency range (Herrmann et al., 2005). Due to the ability to design wavelets to optimise the time-frequency resolution, wavelet analyses are becoming an increasing popular technique for conducting EEG time-frequency analyses. In addition to the ability to modify the wavelet in accordance with the frequency range of interest, an advantage of this technique over the STFT approach is that it does not assume stationarity of the EEG signal (Herrmann et al., 2005). Therefore, on this basis, I chose the wavelet analysis approach to compute the spectral estimates for my ERSP analyses.

Whilst there are numerous wavelets which can potentially be utilised to conduct a variety of analyses of EEG signals, it is important that the wavelet selected is a biologically plausible model of the signal of interest (i.e. representative of the cortical EEG signals). One such wavelet transform, which has become popular for conducting EEG time-frequency analysis, is the Morlet wavelet (Tallon-Baudry et al., 1998). I chose to use the Morlet wavelet approach to conduct the ERSP analysis as it has been shown that this sinusoidal wavelet is effective at detecting sinusoidal EEG activity (Herrmann et al., 2005). Furthermore, Morlet wavelet transforms have previously been used effectively to investigate the oscillatory activity associated with the ANT in an elderly cohort (Deiber et al., 2013).

Morlet wavelet

The Morlet wavelet is a complex wavelet comprising real and imaginary sinusoidal oscillations (of several cycles), that is convolved with a Gaussian envelope function (depicted in Figure 5.1) so that the wavelet magnitude is greatest at the centre (centre time point) and tapers off towards the edges of the time window (Roach, 2008). The Morlet wavelet transform approach involves defining the parameters for the ‘mother wavelet’, this is used to generate additional wavelets (the family of wavelets) which are scaled (compressed and stretched in

the time domain) and shifted versions of the mother wavelet which extend over the frequency range of interest (Roach, 2008).

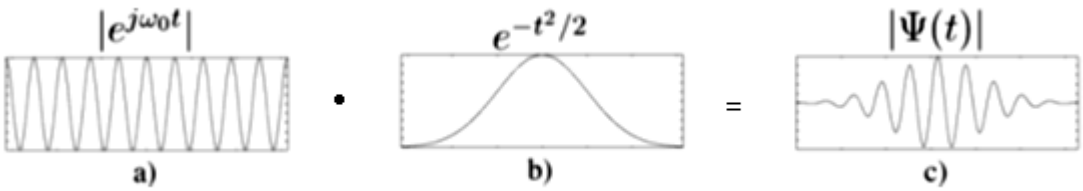


Figure 5.1. Adapted from Herrmann et al. (2005) . In order to derive the Morlet wavelet (c) a sinusoidal function (a) is multiplied with a Gaussian envelope function (b).

The Morlet wavelet can be defined as follows (Herrmann et al., 2005):

$$\varphi(t) = e^{j\omega_0 t} \cdot e^{-t^2/2}$$

$\boldsymbol{j}$ represents the imaginary component

$\boldsymbol{\omega_0}$ equals 2π times the frequency of the mother wavelet

Wavelet transforms are computed as follows: all of the wavelets in the family of wavelets (in this case Morlet wavelets) are convolved with the time series of the EEG signal. A sliding wavelet time window (a scaled mother wavelet) is convolved with the EEG time series, resulting in a new signal comprising complex wavelet coefficients, with real and imaginary components, for each time point across all of the specified frequencies (for each electrode) (Herrmann et al., 2005). These complex data points are used to calculate the spectral decomposition (i.e. magnitude and phase angle) of the EEG data (see Figure 5.2) (Roach & Mathalon, 2008).

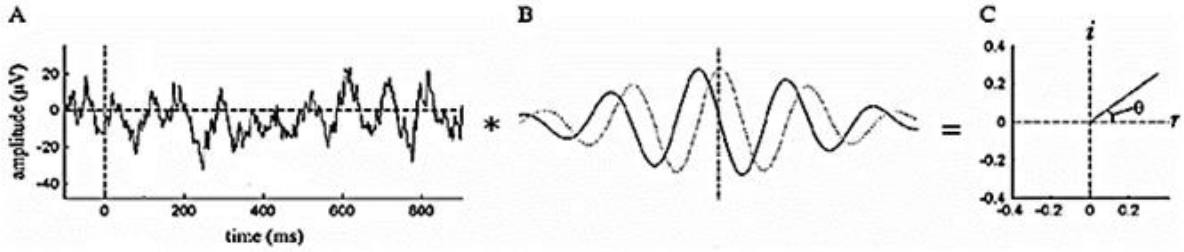


Figure 5.2. Adapted from Roach (2008) **(A)** EEG signal (individual trial), time 0 ms is indicative of stimulus onset **(B)** Complex Morlet wavelet comprising real (solid line) and imaginary (dotted line) wave components, the dashed vertical line depicts the wavelet's centre time point. The EEG signal **(A)** is convolved with the Morlet wavelet **(B)** resulting in **(C)** complex time-frequency data points, each comprising real (depicted by **r**) and imaginary (depicted by **i**) parts. The signal magnitude is represented by the vector length (length from the origin to the complex data point), whilst the phase angle is denoted by the angle of the vector with respect to the x axis.

5.2.2 Morlet Wavelet parameters

Numerous factors must be taken into consideration when designing wavelet analyses, notably the desired frequency and temporal resolution. The resolution (in both time and frequency domains) is constrained by the size (time interval) of the epochs used to conduct the analyses, and the frequency range of interest.

The time intervals for the cue and target epochs were chosen after careful consideration of the intervals needed to conduct a wavelet analysis of my EEG data. Epochs were created using intervals of -600 ms (prior to stimulus onset) to 1500 ms (post-stimulus onset) (as discussed in chapter 4). The time interval of the oscillatory activity of interest was the first 500 ms post-stimulus (cue and target). However, as highlighted by Roach and Mathalon (2008), it is necessary to extract epochs capturing time points beyond the interval of interest to ensure that there are an adequate number of time points for the wavelet applied to the lowest frequency (in our case 4 Hz) once the edges of the time intervals are lost (due to tapering at the edges of the wavelet).

In order to define the Morlet wavelet transform parameters for the time-frequency analyses, EEGLAB newtimef functions were used (Delorme & Makeig, 2004). The number of wavelet cycles used per data time window, which determines the wavelet width (in the time

domain) at each frequency, is a critical parameter in determining the time-frequency decomposition output (Delorme, 2004). Therefore, when designing wavelet analyses, it is crucial to select the most appropriate number of cycles for the data. The optimal number of cycles is driven by the properties of the data mentioned above; including the epoch length, the required time and frequency resolution, and the frequency range of interest. A higher number of cycles results in a wider wavelet (in the time domain) and thus a greater frequency resolution, whilst using a lower number of cycles leads to greater temporal resolution but reduced frequency resolution (Dickter & Kieffaber, 2014).

The wavelet cycle parameters used to conduct my analyses were selected following careful deliberation (and numerous pilot tests) to determine the most appropriate cycle parameters for the data. In the end, the EEGLAB default cycle technique was used; the number of cycles used increased with increasing frequency, thus enabling greater frequency resolution at higher frequencies (Delorme & Makeig, 2004). Although using a greater number of cycles at higher frequencies does, to an extent, diminish the temporal resolution gain associated with the wavelet approach (relative to other time-frequency approaches), the greater frequency resolution at higher frequencies substantially reduces 'blurring effects' which can prove problematic at high frequencies when using fixed cycle wavelet approaches (Dickter & Kieffaber, 2014).

The EEGLAB argument used to define the number of cycles was set to [3 0.5]; the wavelet began with a 3 cycle (3 full sinusoidal cycles) Hanning-tapered window (to remove window border effects) at the lowest frequency of interest which was 4 Hz. Whilst using a higher number of cycles results in greater frequency resolution, 3 cycles is often used in order to enhance the temporal resolution (Roach & Mathalon, 2008).

Given the frequency range (4-90 Hz) and the interval of the data epochs (-600 to 1500 ms) used for my analyses, 3 cycles was deemed to be the optimal number of cycles to use at the lowest frequency in terms of deriving the necessary frequency and temporal resolution. The '0.5' in the EEGLAB argument represents the scaling factor; the number of cycles in the wavelets slowly increased with increasing frequency (up to 100 Hz), until the wavelet width reached half the wavelet width at the lowest frequency (4 Hz) (Dickter & Kieffaber, 2014).

When these cycle parameters were applied to my data, the number of cycles increased linearly from 3 cycles at 4 Hz, to 33.5 cycles at 90 Hz.

5.2.3. ERSP calculations (analyses parameters)

I wrote a MATLAB script, using EEGLAB newtimef functions (Delorme & Makeig, 2004), to conduct wavelet analyses in order to derive estimates of the post-cue and post-target ERSP for each participant. For each participant, average ERSP values were calculated (across all trials) for each cue condition (no cue, neutral, spatial), each target condition (congruent, incongruent), and attentional network effects (alerting, orienting, executive function), for each individual channel as well as each pre-defined region. Refer to chapter 4 for details regarding the channels used to create an average for each of the regions of interest. The mean ERSP for each task condition, and the attentional network effects, was then calculated for each group (controls, AD, DLB).

For all of the ESRP analyses, Morlet wavelets were used to perform the calculations (as discussed in section 5.2.2). For all calculations, epochs with intervals -600 ms to 1500 ms were used (discussed in section 5.2.2), this resulted in a 6 ms time resolution (at each frequency). A frequency range of 4-90 Hz was chosen; 4 Hz was the lowest feasible frequency (determined by the epoch length, cycles and sampling frequency), and is the lowest frequency investigated by comparable studies (Deiber et al., 2013; Fan et al., 2007). The maximum frequency was 90 Hz to enable the post-stimulus oscillatory activity in the gamma range to be investigated, as done by (Fan et al., 2007). The frequency outputs (for statistical analyses) were 172 linearly spaced frequencies between 4-90 Hz (with increments of 0.5 Hz). For the ERSP calculations a baseline interval of -275 to -25 ms pre-stimulus was used (discussed further below).

Baseline calculation

To calculate a post-stimulus ERSP, it is necessary to select a pre-stimulus baseline interval in order to derive changes in the oscillatory activity relative to the pre-stimulus

activity. As with the windowing method used for time-frequency analyses, there is substantial heterogeneity with respect to the baseline methods used for ERSP analyses.

In order to conduct the pre-stimulus baseline calculations, I used the ERSP 'gain model' approach (single trial-based baseline correction method); this is a baseline division technique, for all time-frequency data points the ERSP power was divided by the average spectral power in the baseline interval (mean power across all trials) (Delorme & Makeig, 2004). Using this gain model, it is possible to compute either absolute ERSP values or log-transformed ERSP values. I decided to calculate log-transformed ERSP values (measured in Decibels (dB)) as it has been demonstrated that EEG data tends to be skewed, whilst the logarithm of such signals tends to be more normally distributed than the original EEG signal (prior to log-transformation), thus log transformed (log_{10}) ERSP values are more suitable for subsequent parametric statistical analyses than the absolute ERSP values (Grandchamp & Delorme, 2011). Furthermore, with absolute ERSP values low frequency power changes can mask power changes occurring at higher frequencies, whereas the log transformed values lend themselves to visualisation of a greater frequency range of power perturbations relative to the absolute method (Grandchamp & Delorme, 2011).

The conventional ERSP baseline correction (gain model) approach involves computing the time-frequency decompositions for every trial, followed by calculating the average spectral estimate across all trials, and subsequent removal of the baseline activity. Whilst this technique is widely implemented for ERSP analyses, it has been found to be sensitive to noisy trials (Grandchamp & Delorme, 2011). Recently, a single-trial baseline correction method has been developed (Grandchamp & Delorme, 2011); this involves baseline correction of individual trials prior to averaging spectral estimates across all trials. I decided to use this single-trial baseline correction technique as, relative to the classical baseline correction approach, this method has been found to be more robust to noisy outlier trials, therefore minimising the effect of artefactual trials when estimating the average spectral activity (Grandchamp & Delorme, 2011).

When selecting the baseline interval it is crucial to carefully consider the most appropriate time interval for the data, taking into account the frequency range of interest. Whilst there are no widely accepted conventions for selecting the baseline interval, I decided

to use a 250 ms baseline, as it is recommended that when using a minimum frequency of 4Hz the baseline should be at least 250 ms to capture the activity of the lower frequencies (Roach & Mathalon, 2008). It is also recommended that the baseline should not begin from the start of the epoch due to potential distortions in the signal (as a result of edge effects), and there is debate as to whether to take the baseline interval up to 0 ms (stimulus onset) (Roach & Mathalon, 2008). I therefore decided to use a baseline interval of -275 to -25 ms prior to stimulus onset. Comparable to the baseline method used by Fan et al. (2007), the post-cue ERSPs were calculated using a pre-cue baseline interval (-275 to -25 ms relative to cue onset), whilst the post-target ERSPs were calculated using a pre-target baseline interval (-275 to -25 ms relative to target onset). This pre-target baseline interval was also selected in order to minimise cue-related oscillatory reactivity being encapsulated in the pre-target baseline interval.

5.2.4 Frequency bands

Fan et al. (2007) found associations between the attentional network effects and a wide range of frequencies (in the theta, alpha, beta, and gamma ranges). Therefore, for the statistical analysis of the ERSP data, for each participant (across each task condition) the mean ERSP was calculated for the following fixed frequency bands which span the entire 4-90 Hz frequency interval:

Theta

For the theta band the mean ERSP was calculated between 4-7 Hz (as opposed to 4-8 Hz as used to by Fan et al. (2007)) in order to minimise potential overlap with the alpha frequency band, which is a potentially problematic issue given that DLB patients tend to exhibit a downward shift in their alpha peak frequency (Bonanni et al., 2008)

Alpha

The fixed alpha interval of 8-14 Hz was calculated, the same alpha interval which was used by Fan et al. (2007). In addition to this fixed alpha interval, an individual alpha frequency (IAF; see below), the frequency at which the peak alpha activity occurs, was calculated for each participant. This IAF was calculated in order to control for the variability between participants with respect to the frequency of the peak alpha activity. Calculating the alpha frequency using both of these methods (fixed alpha and IAF) enabled comparison of the results when using these two techniques, thus determining the extent to which group differences are robust (and not merely due to a failure to capture the peak alpha activity with the fixed band method).

Individual alpha frequency (IAF)

It is well documented that inter-individual differences exist regarding the frequency of EEG power spectra (Klimesch, 1999), this is particularly evident within the alpha frequency range. This variability in peak alpha frequency has been termed IAF (individual alpha frequency), where the alpha frequency is computed on an individual basis (Klimesch, 1999). This issue of peak alpha frequency variability is particularly pertinent when investigating task-related oscillatory activity in elderly individuals; peak alpha frequency tends to be lower amongst elderly individuals relative to younger individuals (Grandy, 2013). Furthermore, IAF has been found to be lower amongst dementia patients relative to age-matched healthy controls (Moretti et al., 2004). Consequently, as my ERSP analyses focussed on the between-group comparisons, it was crucial to take the IAF into consideration to ensure that group differences in the alpha frequency band were not merely due to a failure to capture the peak alpha activity.

One of the most commonly used methods to derive the IAF entails calculating the power spectra density (PSD) from resting state EEG recordings, and subsequently visually inspecting the PSD plots to identify the frequency of the individual alpha peak. There are a number of constraints associated with this method; a lack of a clearly-definable peak is a relatively common occurrence, and more than one peak may be evident within the typically

defined alpha frequency range. Furthermore, this method is time consuming as it requires visual inspection of PSD plots for all of the channels of interest, and is highly subjective with respect to assessment of the peak frequency, and therefore the boundary intervals of the alpha range used for subsequent statistical analyses. Recently, a more objective IAF calculation technique has been developed known as the Channel Reactivity Based (CRB) analysis method, developed by Goljahani et al. (2012). The CRB method exploits the reactivity of the alpha rhythms when a participant is engaged in a task. The IAF is calculated using the reactivity of post-stimulus alpha power (test interval) relative to a pre-stimulus interval (rest interval) (Goljahani et al., 2012).

I opted to use the CRB analysis method to calculate the IAF for our participants as this approach ensured that the IAF was representative of the alpha frequency whilst the participants were performing the ANT. In order to implement this analysis, the CRB analysis EEGLAB plugin (Goljahani et al., 2014) was used. For each participant, the IAF was determined by calculating the frequency of the peak alpha reactivity across all channels. For each channel, the channel alpha frequency was calculated, and the overall IAF for a participant was calculated from the alpha frequency of all 128 channels.

The cue epochs were used to derive the PSDs used in calculating the channel alpha frequency; the pre-cue interval of latency -275 ms to -25 ms (prior to cue onset) was selected as the reference (rest) interval, and a test interval of 0 ms to 500 ms (post-cue onset) was chosen. This reference interval was selected as this was the baseline interval for the cue ERSP analyses, and the test interval was selected as it was the post-stimulus interval of interest for the ERSP analyses. Only the cue epochs were used for the PSD estimations given the pre-cue interval was more representative of a 'resting state' than the pre-target interval. PSDs were estimated using the Welsh procedure (Welsh, 1967), with a 50 % overlap between windows to reduce the variance of the PSDs. Hanning windows were used for the estimation of the PSDs in order to reduce spectral leakage (the loss of accurate frequency representation) (Terry & Griffin, 2008). Figure 5.3 shows how the channel alpha frequency (for one channel) was calculated; by superimposing the resting spectrum over the test spectrum the points of intersection of these two plots defined the boundaries for the alpha frequency range for that channel (Goljahani et al., 2012).

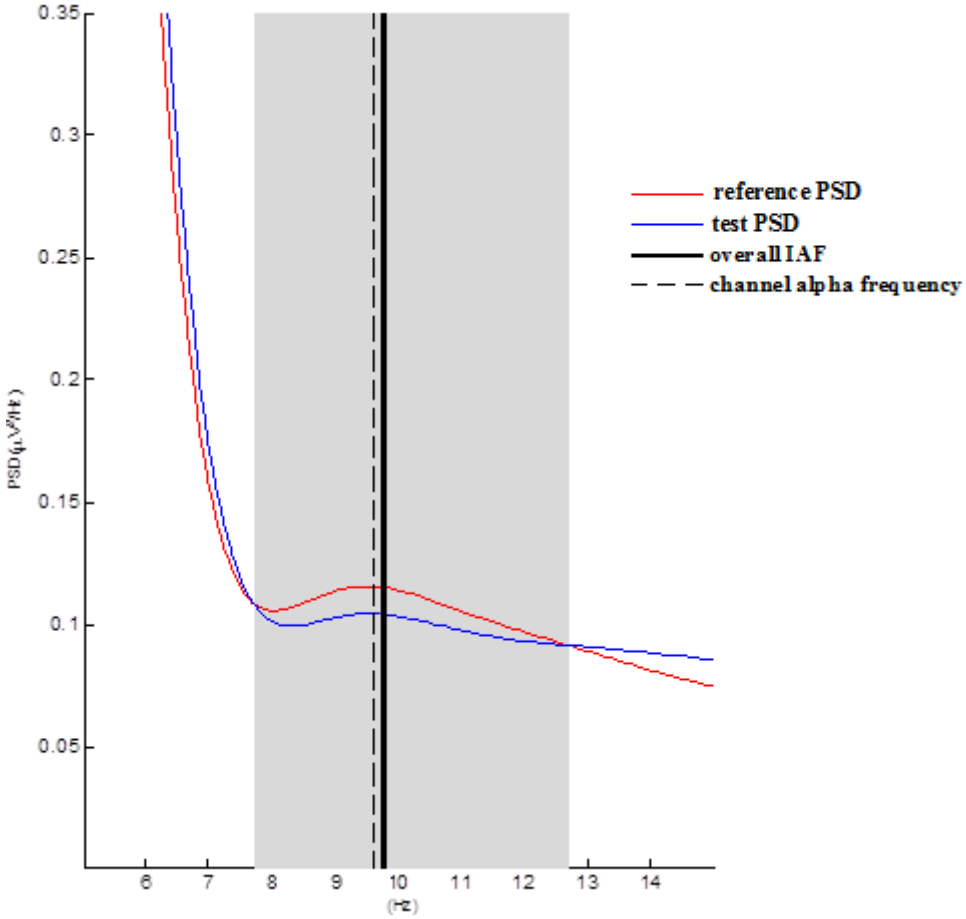


Figure 5.3. Example PSD plot for one electrode (PO9) (one participant), depicting the channel alpha frequency. The red line represents the reference PSD (calculated using the epoch interval -275 to -25 ms (pre-cue)), whilst the blue line depicts the test PSD (calculated using the post-cue 0-500 ms interval). The plot depicts the reference PSD superimposed over the test PSD. The thick vertical black line represents the individual's IAF (individual alpha frequency-calculated using all channels), the dashed vertical black line represents the channel alpha frequency. The responsiveness region (over the alpha frequency range) is shaded in grey. The theta-alpha transition frequency is represented by the lower boundary of the alpha frequency range (the point at which the reference and test PSD plots intersect); for this example electrode the transition frequency is 7.8 Hz.

For each participant, the IAF calculated using the CRB analysis was used to determine the upper and lower alpha boundaries used for the statistical analyses of the individual alpha frequency. As is conventional for IAF analyses (Klimesch, 1999), the upper and lower IAF boundaries were defined as +/- 2 Hz of the IAF respectively. The mean IAF for each group was as follows; controls: 9.9 Hz (SD: 1.24), AD: 9.48 Hz (SD: 1.15), and DLB: 9.13 Hz (SD: 1.33). The mean IAF for the DLB group was significantly lower than that of the controls (p = 0.04), however there was no difference in the mean IAF of the controls and AD group

(p = 0.66), or the AD and DLB groups (p = 1.00). When these values were corrected for multiple comparisons (using Bonferroni correction) the mean IAF difference between the DLB group and controls was no longer significant (p = 0.12).

Beta

The beta frequency band was calculated using an interval of 14-30 Hz, the same interval which was used by Fan et al. (2007).

Gamma

As the data was filtered using a 50 Hz notch filter (discussed in Chapter 4), gamma intervals calculated for subsequent statistical analyses included a low gamma interval (30-45 Hz) and a higher gamma interval (55-90 Hz).

5.2.5 ERSP network effects

As with the behavioural analyses (chapter 3), the ERSPs associated with the network effects were calculated using the equations devised by (Fan et al., 2007):

Alerting effect = neutral cue trials ERSP- no cue trials ERSP

Orienting effect = spatial cue trials ERSP- neutral cue trials ERSP

Executive conflict effect = incongruent target trials ERSP- congruent target trials ERSP

5.2.6 Output data

The raw ERSP data for each participant comprised a series of three dimensional matrices (time x frequency x region); one for each task condition (cues, targets, and network

effects). These ERSP matrices were representative of the mean ERSP across all trials (as opposed to trial by trial), the data values representing the log spectral difference from the baseline interval (measured in dB). I wrote a MATLAB script in order to extract the mean ERSP for each frequency band of interest (theta, alpha, IAF, beta, low gamma and gamma), resulting in a two dimensional ERSP matrix (time x region) for each frequency band, for every task condition (cue and target). Each of these matrices had 80 rows (time) and 7 columns (regions). The time dimension comprised 80 linearly spaced data points representing the ERSP between 0-500 ms post stimulus onset. The region dimension denoted the mean ERSP data in each of the 7 regions of interest, as discussed in chapter 4 (frontal left, frontal right, central left, central right, parietal left, parietal right, and occipital). This data (for each participant) was then exported to SPSS for subsequent statistical analyses.

5.2.7 Statistical analysis

All statistical analyses were conducted using SPSS 19.0 (SPSS Inc, Chicago), and an alpha value of 0.05. Separate analyses were performed for each task condition; cue (no cue, neutral cue, spatial cue), target (congruent, incongruent), and attentional network effects (alerting, orienting, executive conflict). For each of these task conditions, the analyses for each of the frequency bands (theta, alpha, IAF, beta, low gamma, gamma) were conducted separately. As the ERSP data imported from MATLAB comprised 80 linearly spaced time points spanning the 0-500 ms interval (see section 5.2.6), to limit the number of statistical comparisons the mean ERSP was calculated for each successive 50 ms interval, resulting in 10 time points. Repeated measures ANOVAs were conducted with region (7 levels) and time (10 levels) as within-subject factors and group (controls, AD, DLB) as a between-subject factor. This method is comparable to that of Deiber et al (2013), although they used 200 ms time intervals. I choose to use 50 ms intervals as this was deemed to be a sufficient time interval to encapsulate the activity in the frequency range of interest, particularly the higher frequencies in the gamma range, in which the ERSP activity tends to be evident over shorter time intervals relative to the ERSP in the lower frequencies. As the groups were well matched in terms of demographics (section 5.3), it was not necessary to covary for demographic variables in the analyses. Given that that cholinesterase inhibitor usage in dementia cohorts

has been shown to enhance attentional function (Emre et al., 2004; McKeith et al., 2000a) medication usage (cholinesterase and dopaminergic medication usage) was initially considered as a covariate in the analyses models, however, as with the behavioural analyses (chapter 3), there were no significant main effects or interactions. Mauchly's sphericity test was used for all ANOVAs and non-sphericity corrected for where appropriate. Post-hoc analyses were conducted to determine group differences for each time point (each 50 ms) using pairwise comparisons. Bonferroni correction was used to correct for family-wise errors due to multiple comparisons for all the above analyses.

Post-hoc Pearson's *r* correlations (two tailed) were performed between the ERSP associated with each of the attentional network effects and key clinical variables. The clinical variables comprised cognitive fluctuation measures (CAF, MFS), as well as measures of global cognitive functioning (MMSE and CAMCOG), and the UPDRS. In addition, correlation analyses between the network ERSP and the participants' overall mean RT and the corresponding behavioural network effect were conducted. All correlation analyses were exploratory, and were thus uncorrected for multiple comparisons and were, in the main, examined only when there were significant group differences between the ERSP values, although there were several *a priori* defined comparisons on the basis of my hypotheses (section 5.1.2).

5.3 Participants

The participant cohort comprised 19 controls, 24 AD patients, and 22 DLB patients. The demographics of the cohort are described in Table 5.1. The groups were well matched in terms of age, gender and level of education. The dementia groups (AD and DLB) were matched in terms of age of onset and duration of the cognitive symptoms associated with the condition. There were no significant differences between the dementia groups with respect to MMSE, CAMCOG or NPI total scores (Table 5.1). The medication usage of the dementia patients is detailed in Table 5.2. The time since the last dose of Levodopa (prior to testing) was between 1-3 hours (consistent across participants).

Table 5.1. Demographics (means, and standard deviations in brackets) of the participants included in the time-frequency analyses. Note: the 'Dementia groups' column shows the results of analyses comparing the AD and DLB groups only.

	Controls (n=19)	**AD (n=24)**	**DLB (n=22)**	**All groups**	**Dementia groups**
Age (years)	76.37 (5.45)	75.79 (8.27)	75.73 (6.58)	$F(2, 62) = 0.05$, $p = 0.95$	$F(1, 44) = 0.01$, $p = 0.98$
Gender (female, male)	6, 13	5, 19	4, 18	$\chi^2(2, N=65) = 1.14$, $p = 0.57$	$\chi^2(1, N=46) = 0.51$, $p = 0.56$
Education level[1]	2.70 (0.94)	2.38 (0.71)	2..27 (0.88)	$F(2, 65) = 2.07$, $p = 0.14$	$F(1,44) = 0.19$, $p = 0.66$
Condition (cognitive symptoms) *age at onset*	-	71.88 (8.31)	72.23 (8.05)	-	$F(1, 44) = 0.02$, $p = 0.89$
duration (years)	-	3.91 (2.07)	3.46 (2.28)	-	$F(1,44) = 0.29$, $p = 0.60$
MMSE[2] total	29.21 (0.86)	21.88 (3.17)	23.18 (3.97)	$F(2,62) = 33.70$, $p < 0.001$**	$F(1,44) = 1.54$, $p = 0.22$
CAMCOG[3] total	96.84 (3.75)	72.00 (11.49)	75.59 (12.97)	$F(2, 62) = 33.36$, $p < 0.001$**	$F(1,44) = 0.99$, $p = 0.33$
UPDRS[4] total	1.16 (1.46)	2.13 (2.03)	16.82 (7.02)	$F(2,62) = 88.54$, $p < 0.001$*	$F(1,44) = 96.50$, $p < 0.001$**
CAF[5] total	-	0.87 (1.79)	3.27 (3.98)	-	$F(1,43) = 6.93$, $p = 0.01$*
MFS[6] total		9.17 (3.80)	11.18 (6.43)	-	$F(1,43) = 1.65$, $p = 0.21$
NPI[7] total	-	7.65 (6.60)	8.68 (5.20)	-	$F(1,43) = 0.34$, $p = 0.57$
Cornell depression scale[8]	0.67 (1.21)	1..21 (1.29)	1.68 (1.39)	$F(2,61) = 3.09$, $p = 0.05$	$F(1,44) = 1.44$, $p = 0.24$

**** $p < 0.001$, * $p < 0.05$**

[1]**Years of education rating scale**: 1 = < 9 years, 2 = 9-11 years, 3 = 12-13 years, 4 = 14+ years, [2]**MMSE** = Mini Mental State Examination (Folstein et al., 1975), [3]**CAMCOG =** Cambridge Cognitive Examination (Roth et al, 1988), [4] **UPDRS =** Unified Parkinson's disease rating scale (motor subscale) (Fahn et al, 1987), [5]**CAF =** Clinician Assessment of Fluctuations (Walker et al, 2000), [6]**MFS =** MAYO Fluctuation Scale (Ferman et al., 2004), [7]**NPI =** Neuropsychiatric Inventory (Cummings et al., 1994), [8] **Cornell depression scale** (Alexopoulos et al., 1988).

The following Bonferroni corrected pairwise comparisons indicate the significant group differences listed in Table 5.1:

[2] **MMSE** = Mini Mental State Examination

*controls > AD (p <0.001), controls > DLB (p <0.001)

[3] **CAMCOG** = Cambridge Cognitive Examination

* controls > AD (p <0.001), controls > DLB (p <0.001)

[4] **UPDRS** = Unified Parkinson's disease rating scale (motor subsection)

* DLB > AD (p <0.001), DLB > controls (p <0.001)

[5] **CAF** = Clinician Assessment of Fluctuations

*DLB > AD (p = 0.01)

Table 5.2. Medication usage of the time-frequency analyses patient cohort

	AD (n=24)	**DLB (n=22)**
cholinesterase inhibitors	22 (92 %)	21 (95 %)
dopaminergic medication	-	9 (41 %)
antipsychotics	-	1 (5 %)
SSRIs	3 (13 %)	5 (23 %)

5.4 ERSP results layout

The results of the ERSP elicited during each of the cue and target task conditions are reported in chapter 6, and the attentional network ERSP analyses results are described in chapter 7. In addition, brief behavioural analyses were conducted in order to ensure that task performance of the participants included in the EEG analyses was comparable to that of the larger participant cohort discussed in chapter 3. The behavioural results corresponding to the cue and target conditions are presented in chapter 6, whilst the behavioural results associated with each of the attentional network effects are reported in chapter 7. For clarity, the ERSP results (for each task condition and each of the attentional network effects) are presented in the following order:

- Time-frequency decomposition plots (for each group) depicting the ERSP for the post-stimulus 500 ms across the whole frequency range (4-90 Hz).
- A table showing the results of the repeated measures ANOVAs for the ERSP associated with each frequency band (theta, alpha, IAF, beta, low gamma, gamma).
- A brief description of the ERSP for each group based on visual inspection of the time-frequency decomposition plots.
- Following the brief plot description, only significant results and statistical trends ($p \leq 0.10$) from the ANOVA results table are discussed further in the text. Power plots showing the ERSP across each region are presented for significant results. For clarity error bars are not shown on these plots, however the significant differences between each group (results of post-hoc Bonferroni corrected pairwise comparisons) are depicted. Power plots are shown for all frequency bands in which there were significant effects, irrespective of whether there was a time x region x group interaction, as they are a useful indicator of the general trends in the data (although the plots are discussed in the context of the significant effects given in the ANOVA table). In the text, visual inspection is used to give a brief explanation of significant time and region effects (independent of group), whilst the group effects are explained in detail and the corresponding p values given.
- In chapter 7, for the correlation analyses between the attentional network effects and key clinical variables only significant results are presented. As described in section 5.2.7, these exploratory analyses were largely driven by the significant group differences in the ERSP for each of the networks.

Chapter 6 . Oscillatory reactivity results: cue and target

6.1 Behavioural results

The mean RTs of the participant cohort included in the ERSP analyses, for each cue and target condition, are shown in Table 6.1.

Table 6.1. Mean reaction times (RT) (correct responses) for each task condition (ms), and overall mean RT (across all task conditions), for each group. Standard deviations are presented in italics. The ANOVA results (Bonferroni corrected) show significant group differences for each condition.

	Cohort			**All group comparison**
	Controls (n=19)	**AD (n=24)**	**DLB (n=22)**	
overall mean RT	962.47 *(151.09)*	1296.83 (*307.77*)	1431.10 *(349.43)*	$F(2,62) = 14.00,\ p < 0.001$*
Cue				
no cue	1024.08 *(168.82)*	1346.07 *(312.24)*	1504.81 *(400.21)*	$F(2,62) = 12.16,\ p < 0.001$*
neutral	982.26 *(152.06)*	1331.72 *(310.93)*	1482.40 *(393.38)*	$F(2,62) = 13.86,\ p < 0.001$*
spatial	886.89 *(138.17)*	1252.30 *(339.87)*	1418.17 (*374.55*)	$F(2,62) = 15.42,\ p < 0.001$*
Target				
congruent	774.05 *(95.10)*	1017.87 *(242.24)*	1110.62 *(269.18)*	$F(2,62) = 19.68,\ p < 0.001$*
incongruent	1154.58 *(230.23)*	1603.52 *(415.32)*	1725.00 *(507.95)*	$F(2,62) = 10.81,\ p < 0.001$*

***** All significant group differences (Bonferroni corrected pairwise comparisons) are detailed below:

overall mean RT: controls < AD (p <0.01), controls < DLB (p <0.001)

no cue: controls < AD (p = 0.01), controls < DLB (p <0.001)

neutral cue: controls < AD (p = 0.01), controls < DLB (p <0.001)

spatial cue: controls < AD (p = 0.01), controls < DLB (p <0.001)

congruent target: controls < AD (p <0.01), controls < DLB (p <0.001), AD < DLB (p = 0.02)

incongruent target: controls < AD (p <0.01), controls < DLB (p <0.001)

As shown in Table 6.1, for each of the cue and target conditions the controls had a faster mean RT relative to the AD and DLB groups. For the cue conditions, there was no difference between the mean RT of the two dementia groups. With regard to the target conditions, there was no difference between the mean RT of the two dementia groups for the incongruent target trials, however the AD group exhibited a faster mean RT for the congruent target trials relative to the DLB group. The RTs for each group are broadly comparable to those reported in chapter 3. In terms of overall mean RT (across all task conditions), the control group mean RT was faster than that of the DLB and AD groups, however there was no difference between the overall mean RT of the AD and DLB patients. Whilst the behavioural results in chapter 3 showed a faster overall mean RT in the control group relative to the dementia groups, the AD group was also faster overall than the LBD group. Given that overall mean RT slowing in the LBD cohort (chapter 3) correlated with UPDRS total score, the lack of difference between the AD and DLB overall mean RT is explicable in terms of the more motor impaired PDD patients' data being excluded from the analyses reported in Table 6.1.

6.2. Cue-locked ERSP

6.2.1 No cue

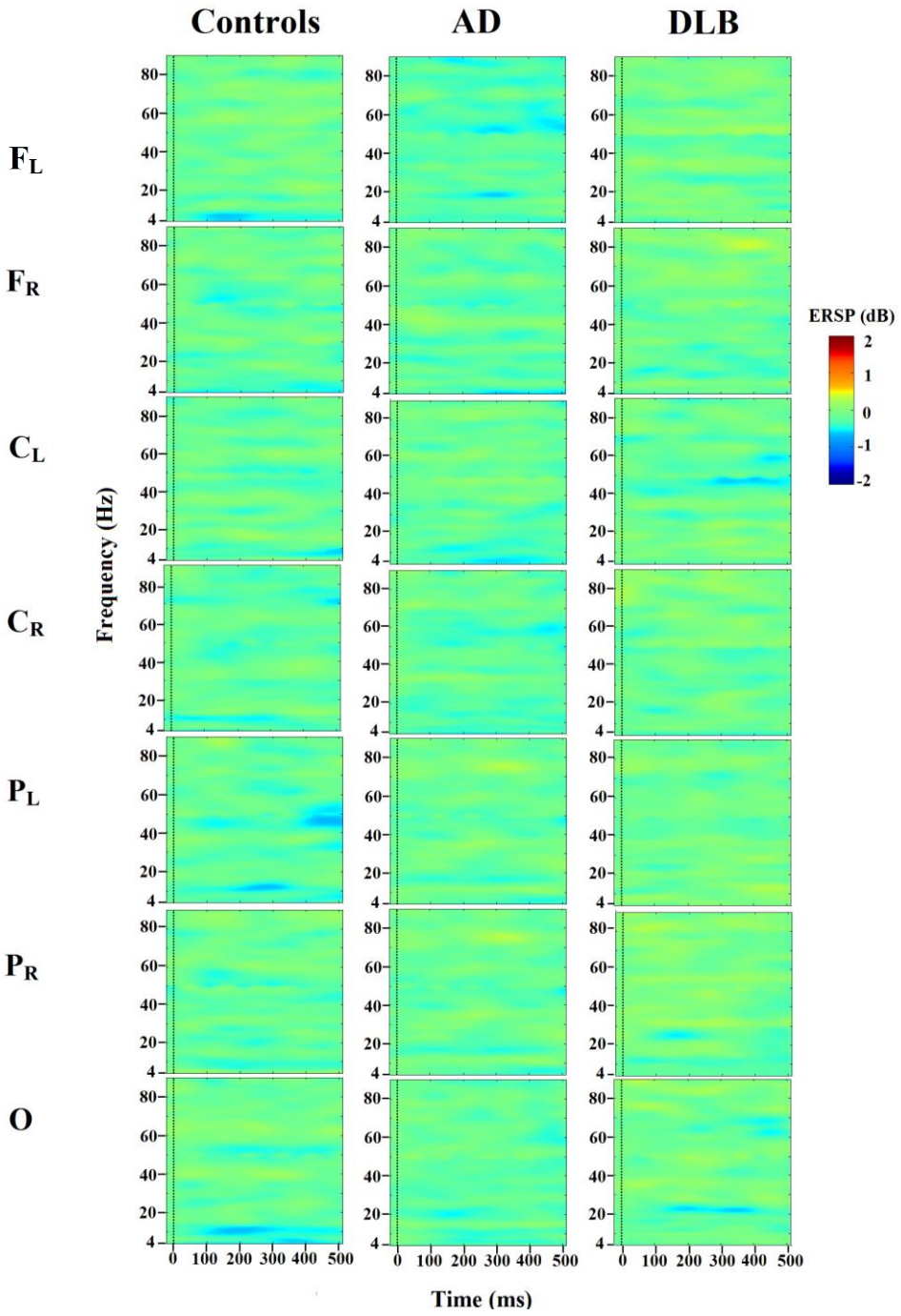


Figure 6.1. Heat maps showing time-frequency ERSP (event-related spectral perturbation) for the no cue condition, for each group (controls, AD, DLB), across each region. Power (dB) is plotted in colour (see scale); positive values represent event-related synchronisation, negative values represent event-related desynchronisation. The x axes represent time (ms) post-cue (no cue) presentation, the vertical line at time 0 ms denotes the onset of the no cue trigger. The Y axes represent frequency (Hz) depicted from 4-90 Hz. F_L = Frontal left hemisphere, FR = Frontal right hemisphere, C_L= Central left hemisphere, C_R = Central right hemisphere, P_L = Parietal left hemisphere, P_R = Parietal right hemisphere, O = Occipital region.

Table 6.2. Results of the no cue ERSP repeated measures ANOVAs for each frequency band. The ANOVAs were conducted separately for each frequency band, with group (controls, AD, DLB) as the between-subjects factor, and time (10 intervals) and region (7 regions) as within-subject variables. Confidence intervals were adjusted using Bonferroni correction.

	Frequency band					
ANOVA factor	**Theta (4-7 Hz)**	**Alpha (8-14 Hz)**	**IAF (Individual alpha frequency)**	**Beta (14-30 Hz)**	**Low gamma (30-45 Hz)**	**Gamma (55-90 Hz)**
time	$F(2.1, 133.6) = 1.27$, $p = 0.28$	$F(3.1, 190.8) = 1.25$, $p = 0.29$	$F(2.5, 152.9) = 2.11$, $p = 0.11$	$F(3.0, 186.3) = 1.00$, $p = 0.39$	$F(3.3, 205.1) = 0.97$, $p = 0.41$	$F(3.6, 224.7) = 1.98$, $p = 0.11$
region	$F(6, 372) = 1.44$, $p = 0.20$	$F(6, 372) = 2.03$, $p = 0.06$	$F(6, 372) = 1.00$, $p = 0.42$	$F(6, 372) = 0.95$, $p = 0.46$	$F(6, 372) = 0.34$, $p = 0.92$	$F(6, 372) = 0.95$, $p = 0.46$
time x region	$F(12.9, 798.8) = 1.16$, $p = 0.31$	$F(15.1, 938.7) = 0.92$, $p = 0.55$	$F(12.5, 773.3) = 0.47$, $p = 0.94$	$F(16.4, 1018.0) = 1.42$, $p = 0.12$	$F(16.3, 1012.6) = 0.56$, $p = 0.92$	$F(16.7, 1037.5) = 1.09$, $p = 0.36$
group	$F(2, 62) = 2.87$, $p = 0.60$	$F(2, 62) = 4.10$, $p = 0.02$*	$F(2, 62) = 4.10$, $p < 0.01$*	$F(2, 62) = 1.81$, $p = 0.17$	$F(2, 62) = 0.78$, $p = 0.47$	$F(2, 62) = 2.20$, $p = 0.12$
time x group	$F(4.3, 133.6) = 0.84$, $p = 0.51$	$F(6.2, 190.8) = 0.65$, $p = 0.69$	$F(4.9, 152.9) = 0.65$, $p = 0.69$	$F(6.0, 186.3) = 1.17$, $p = 0.28$	$F(6.6, 205.1) = 0.39$, $p = 0.90$	$F(7.2, 224.7) = 0.94$, $p = 0.48$
region x group	$F(12, 372) = 1.20$, $p = 0.28$	$F(12, 372) = 1.56$, $p = 0.10$	$F(12, 372) = 0.65$, $p = 0.80$	$F(12, 372) = 0.65$, $p = 0.79$	$F(12, 372) = 1.18$, $p = 0.30$	$F(12, 372) = 2.08$, $p = 0.02$*
time x region x group	$F(25.8, 798.8) = 0.86$, $p = 0.66$	$F(30.3, 938.7) = 0.94$, $p = 0.57$	$F(24.9,773.3) = 0.75$, $p = 0.81$	$F(32.8, 1018.0) = 1.55$, $p = 0.30$	$F(32.7, 1012.6) = 0.93$, $p = 0.58$	$F(33.5, 1037.5) = 1.00$, $p = 0.47$

* = $p < 0.05$

= Statistical trend ($p \leq 0.10$)

No cue plot overview

The time-frequency decomposition plots for the post-no cue (absence of a stimulus) 500 ms interval, for each group, are depicted in Figure 6.1. In this 500 ms interval, across the whole frequency range of interest (4-90 Hz), it is evident that in each of the groups there was relatively little change in the oscillatory activity with respect to the baseline interval (as would be expected given the no cue condition denotes the absence of stimulus presentation). In the controls, it is apparent there was ERD in the low frequencies (theta/alpha range) in the occipital, and left parietal and frontal regions. In addition, there was an observable ERD in the gamma range which was most visible in the left parietal region between 40-60 Hz. The AD and DLB groups also exhibited ERDs, however the regions in which these occurred differed with respect to the controls. The AD group ERDs were most prominent in the left frontal region in the beta and gamma ranges, whilst in the DLB group there was ERD in the left central left region in the low gamma range, and also in the occipital beta range. As discussed in chapter 5 (section 5.4) only significant results for each task condition are discussed in detail, and thus based on the results in Table 6.2, the no cue ERSP for the alpha and gamma (55-90 Hz) bands are described below.

No cue alpha ERSP

Table 6.2 shows that there was a main effect of group in the alpha frequency range, this was significant for both the fixed frequency alpha band and the IAF. The power plots for each are presented in Figures 6.2 and 6.3 respectively.

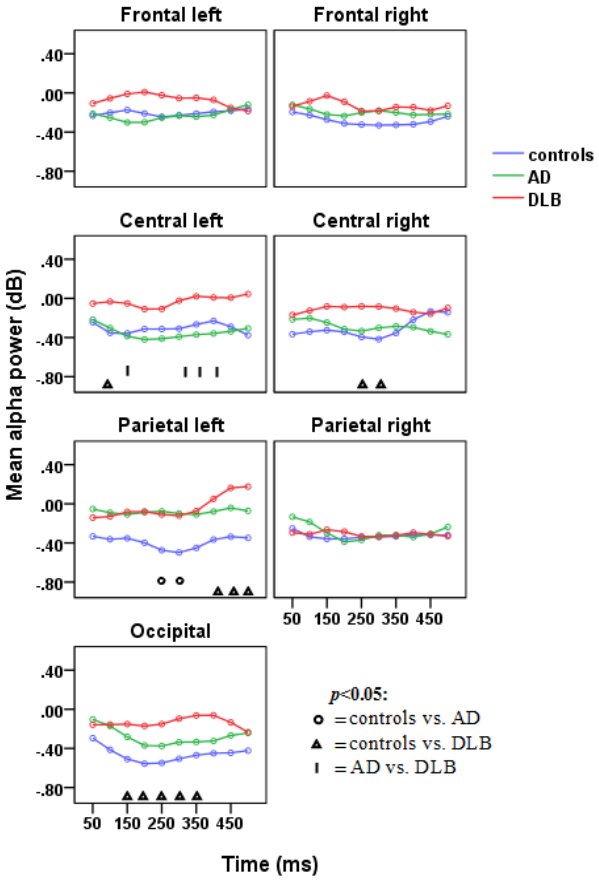


Figure 6.2. Mean alpha power (dB) for the post-no cue 500 ms interval across each region, for each group (controls, AD, DLB). The time points at which significant differences (p <0.05) between groups occurred are depicted on the plots (after correcting for multiple comparisons using Bonferroni correction).

For the fixed alpha frequency band, the main effect of group was due to greater ERD (across all regions for the whole 500 ms time interval of interest) in the controls relative to the DLB group (p = 0.02), whilst there was no difference between the DLB and AD ERSP (p = 0.21), or the controls and AD ERSP (p = 0.83). For the IAF, as with the fixed alpha band, there was greater ERD in the controls relative to the DLB group (p <0.001), and no significant difference between the AD and control groups (p = 0.37); however the ERD was greater in the AD group relative to the DLB group (p = 0.03). From Figures 6.2 and 6.3 it is evident that the ERSP (for each group) was fairly comparable across regions, and across the whole 500 ms, hence the lack of overall time and region effects (for both fixed alpha and IAF). The trend for a region effect for the fixed alpha band (Table 6.2) is evident from Figure 6.2; there was less ERSP in the frontal regions (bilaterally) and right parietal region relative to the other regions.

The overall group interactions were not significant for the alpha range, however there was a trend for a region x group interaction when using the fixed alpha band (Table 6.2). The results of exploratory post-hoc analyses of significant group differences are depicted in Figures 6.2 and 6.3. There was some variability between the fixed alpha and IAF regarding group differences, although overall both approaches suggested there was less ERD in the DLB group relative to the controls at 100 ms in the left central region, 450-500 ms in the left parietal region, and between 150-350 ms in the occipital region.

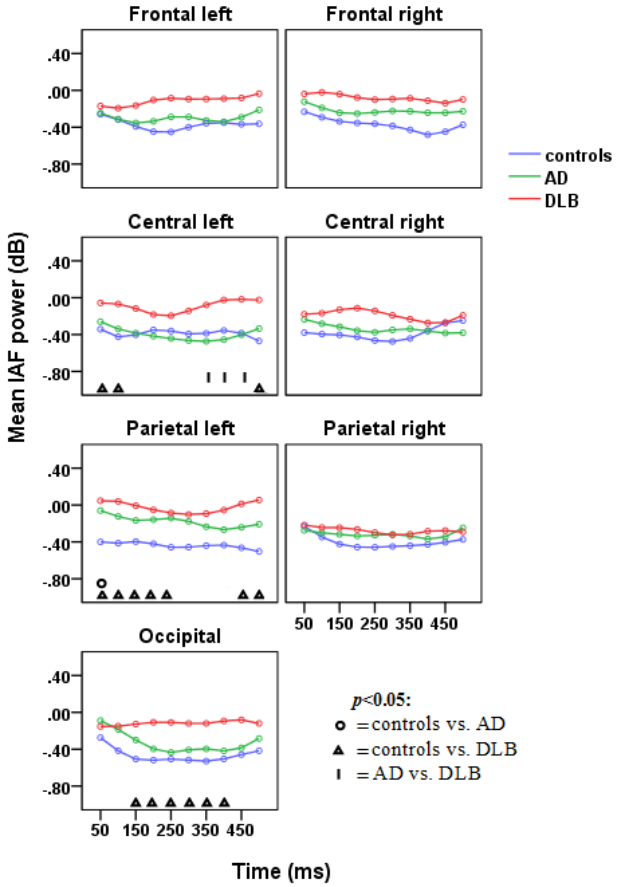


Figure 6.3. Mean IAF (individual alpha frequency) power (dB) for the post-no cue 500 ms interval across each region, for each group (controls, AD, DLB). The time points at which significant differences (p <0.05) between groups occurred are depicted on the plots (after correcting for multiple comparisons using Bonferroni correction).

No cue gamma ERSP

As shown in Table 6.2, there was a significant group x region interaction for the 55-90 Hz gamma range ERSP. The left frontal region was the only region in which the mean ERSP (independent of time) was significantly different between the groups; there was greater ERD in the AD group relative to the DLB group (p = 0.03) in this region, however there was no difference between the controls and AD ERSP (p = 0.08), or the controls and DLB ERSP (p = 1.00).

The results of the exploratory post-hoc analyses (for each time point), depicted in Figure 6.4, show that group differences were evident bilaterally in the frontal and parietal regions; primarily greater ERD in the AD group relative to the DLB group, although there was less ERD in the AD group relative to controls in the left parietal region.

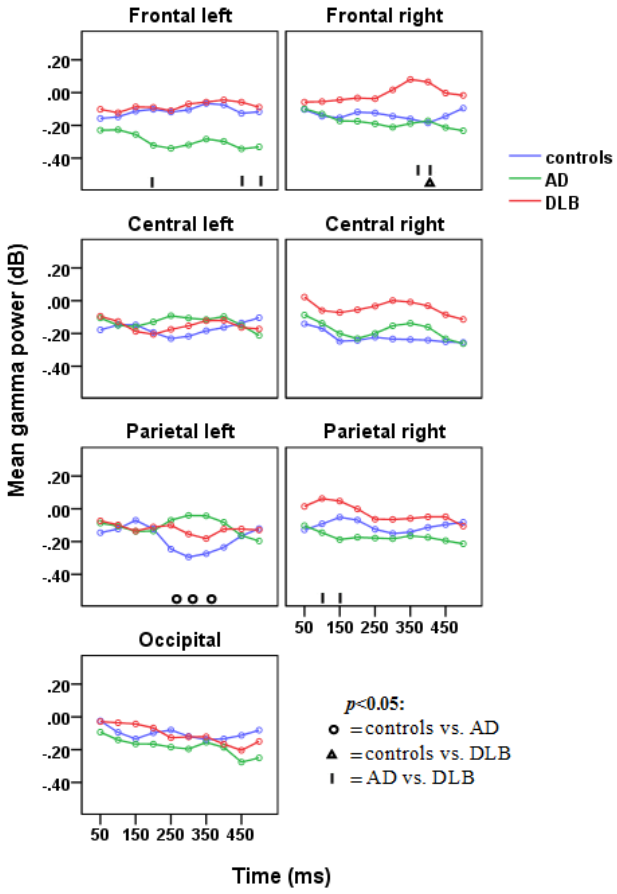


Figure 6.4. Mean gamma (55-90 Hz) power (dB) for the post-no cue 500 ms interval across each region, for each group (controls, AD, DLB). The time points at which significant differences (p <0.05) between groups occurred are depicted on the plots (after correcting for multiple comparisons using Bonferroni correction).

No cue ERSP summary

- In the absence of a cue, reactivity differences between the dementia patients and controls were evident in the alpha and gamma frequency bands only.
- In the alpha band, for both the fixed alpha and IAF, there was a main effect of group. There was degree of heterogeneity between the fixed alpha and IAF regarding the significance of group differences, although both approaches suggested less ERD (across all regions, independent of time) in the DLB group relative to the controls. Therefore, it is reasonable to assume that this significant difference is a robust finding (as it was evident using both techniques).
- In the 55-90 Hz gamma band, the region x group interaction (independent of time) was due to greater ERD in the AD group relative to the DLB group in the left frontal region.
- The lack of significant time effects (Table 6.2) was expected given that the no cue condition denotes an absence of stimulus presentation. The ERSP in the post-no cue interval can be considered to be an indicator of the activity associated with anticipatory attention (for the upcoming target stimulus), therefore the group differences (for both the alpha and gamma band) may be associated with group differences in anticipatory attention.

6.2.2 Neutral cue

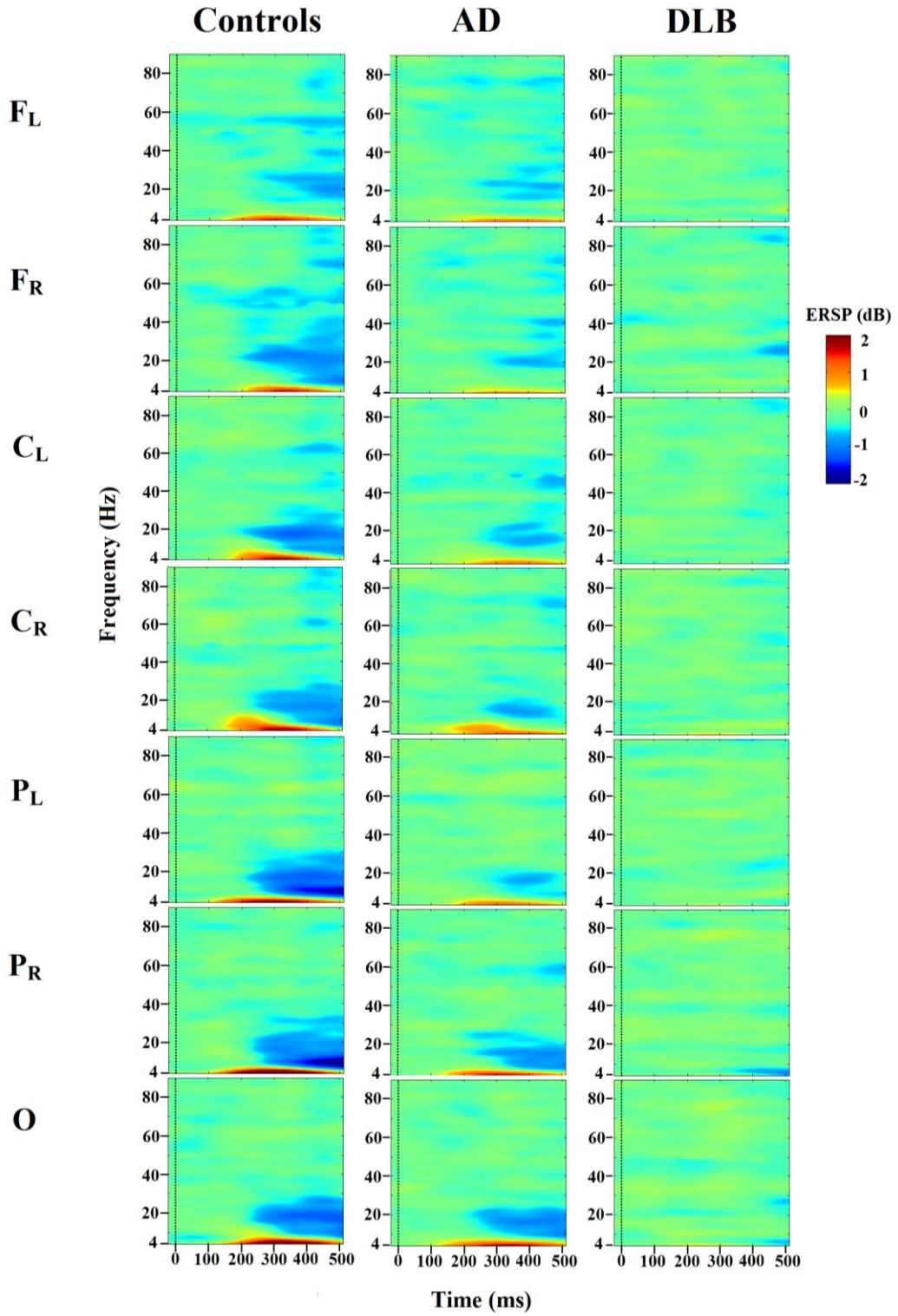


Figure 6.5. Heat maps showing time-frequency ERSP (event-related spectral perturbation) for the neutral cue condition, for each group (controls, AD, DLB), across each region. Power (dB) is plotted in colour (see scale); positive values represent event-related synchronisation, negative values represent event-related desynchronisation. The x axes represent time (ms) post-cue presentation, the vertical line at time 0 ms denotes the onset of the cue. The Y axes represent frequency (Hz) depicted from 4-90 Hz. F_L = Frontal left hemisphere, FR = Frontal right hemisphere, C_L= Central left hemisphere, C_R = Central right hemisphere, P_L = Parietal left hemisphere, P_R = Parietal right hemisphere, O = Occipital region.

Table 6.3. Results of the neutral cue ERSP repeated measures ANOVAs for each frequency band. The ANOVAs were conducted separately for each frequency band, with group (controls, AD, DLB) as the between-subjects factor, and time (10 intervals) and region (7 regions) as within-subject variables. Confidence intervals were adjusted using Bonferroni correction.

	Frequency band					
ANOVA factor	**Theta (4-7 Hz)**	**Alpha (8-14 Hz)**	**IAF (Individual alpha frequency)**	**Beta (14-30 Hz)**	**Low gamma (30-45 Hz)**	**Gamma (55-90 Hz)**
time	$F(1.9, 119.1) = 41.9$, $p < 0.001$**	$F(1.9, 117.4) = 16.46$, $p < 0.001$**	$F(1.8, 110.1) = 17.07$, $p < 0.001$**	$F(1.7, 107.7) = 45.53$, $p < 0.001$**	$F(3.5, 214.6) = 11.0$, $p < 0.001$**	$F(3.1, 189.8) = 6.81$, $p < 0.001$**
region	$F(5.1, 314.1) = 3.15$, $p = 0.01$*	$F(6, 372) = 3.62$, $p < 0.01$*	$F(6, 372) = 5.01$, $p < 0.001$**	$F(6, 372) = 5.56$, $p = 0.75$	$F(6, 372) = 1.51$, $p = 0.18$	$F(6, 372) = 2.57$, $p = 0.02$*
time x region	$F(10.4, 643.5) = 3.16$, $p < 0.001$**	$F(12.6, 783.4) = 6.22$, $p < 0.001$**	$F(10.9, 678.79) = 5.32$, $p < 0.001$**	$F(13.6, 844.6) = 1.24$, $p = 0.25$	$F(15.4, 953.3) = 2.36$, $p < 0.01$*	$F(16.0, 989.3) = 3.35$, $p < 0.001$**
group	$F(2, 62) = 10.33$, $p < 0.001$**	$F(2, 62) = 1.15$, $p = 0.32$	$F(2, 62) = 1.15$, $p = 0.32$	$F(2, 62) = 7.15$, $p < 0.01$*	$F(2, 62) = 3.25$, $p = 0.05$	$F(2, 62) = 1.31$, $p = 0.28$
time x group	$F(3.8, 11.0) = 7.45$, $p < 0.001$**	$F(3.8, 117.4) = 5.88$, $p < 0.001$**	$F(3.6, 110.1) = 3.40$, $p < 0.001$**	$F(3.5, 107.7) = 7.44$, $p < 0.001$**	$F(6.9, 214.6) = 0.85$, $p = 0.55$	$F(6.12, 189.8) = 1.42$, $p = 0.21$
region x group	$F(10.1, 314.1) = 1.13$, $p = 0.34$	$F(12, 372) = 2.34$, $p = 0.01$*	$F(12, 372) = 0.89$, $p = 0.55$	$F(12, 372) = 0.88$, $p = 0.57$	$F(12, 372) = 0.30$, $p = 0.99$	$F(12, 372) = 1.42$, $p = 0.17$
time x region x group	$F(20.8, 643.5) = 1.72$, $p = 0.03$*	$F(25.3, 783.4) = 2.13$, $p < 0.01$*	$F(21.9, 678.79) = 1.59$, $p = 0.04$*	$F(27.2, 844.6) = 1.03$, $p = 0.42$	$F(30.8, 953.3) = 0.96$, $p = 0.53$	$F(31.9, 989.3) = 1.19$, $p = 0.22$

* = $p < 0.05$

Neutral cue plot overview

Figure 6.5 shows that in the control group the oscillatory activity associated with the presentation of the neutral cue included a low frequency (theta/alpha) ERS which was evident across all regions from approximately 100-200 ms. This low frequency ERS was also apparent in the AD group across all regions (albeit to a lesser extent than the controls), however it was not evident in the DLB group. In the controls, across all regions, there was a broad ERD in the alpha/beta/low gamma range, with an onset of approximately 200 ms (this varied according to region). This ERD was also apparent in the AD group but was diminished relative to controls. In the DLB group this ERD was largely absent, although there was some ERD in the right frontal, right parietal and occipital regions between approximately 350-500 ms. In the controls there were intervals of ERD in the higher gamma range (55-90 Hz), particularly in the frontal and central regions, which were diffuse across both the gamma range and time domain (occurring predominantly in the latter half of the 500 ms interval). Areas of ERD were also apparent in the AD group in comparable regions to the controls, however the only clear ERD in the DLB group was in the right frontal region between approximately 80-90 Hz in the 400-500 ms interval.

Neutral cue theta ERSP

The main effect of time (Table 6.3) was explicable in terms of the theta ERS which occurred across all regions and peaked at approximately 300-350 ms (as depicted in Figure 6.6). However, variability across regions with respect to the time at which this ERS peaked accounted for the significant time x region interaction. Table 6.3 shows there was also a significant main effect of region (across all groups), as is evident in Figure 6.6 this was due to greater ERS power in posterior regions (particularly right parietal and occipital regions) relative to frontal regions.

There was a main effect of group (Table 6.3); across all regions (independent of time) the mean ERS power was greater in the controls relative to both the AD group (p <0.01) and DLB group (p <0.001), however there was no difference in the mean ERS between the AD and DLB groups (p = 0.84). The time intervals in which this DLB group ERS was significantly less than that of the controls were fairly consistent across regions (Figure 6.6), encompassing the vast majority of the 500 ms interval in the parietal regions (with the

exception of the initial 100 ms following the neutral cue onset). The only significant difference between the controls and AD group was in the occipital region; there was greater ERD in the controls relative to the AD group in the initial 100 ms. From Figure 6.6, it is clear that there were several consecutive time points in the left central, right parietal and occipital regions where the DLB ERS was less than that of both the AD and control groups, thus signifying the aberrant theta activity which differentiated the DLB group from the controls and AD group.

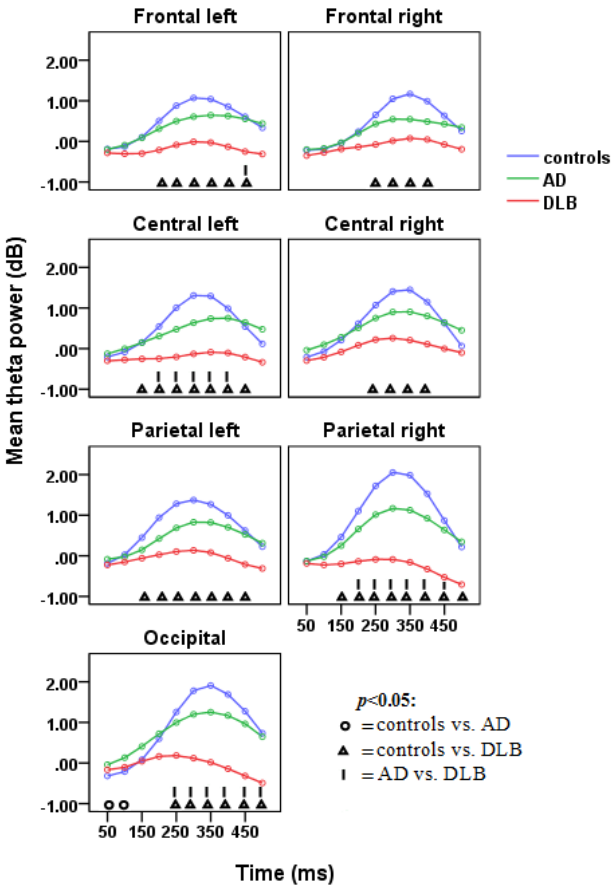


Figure 6.6. Mean theta power (dB) for the post-neutral cue 500 ms interval across each region, for each group (controls, AD, DLB). The time points at which significant differences (p <0.05) between groups occurred are depicted on the plots (after correcting for multiple comparisons using Bonferroni correction).

Neutral cue alpha ERSP

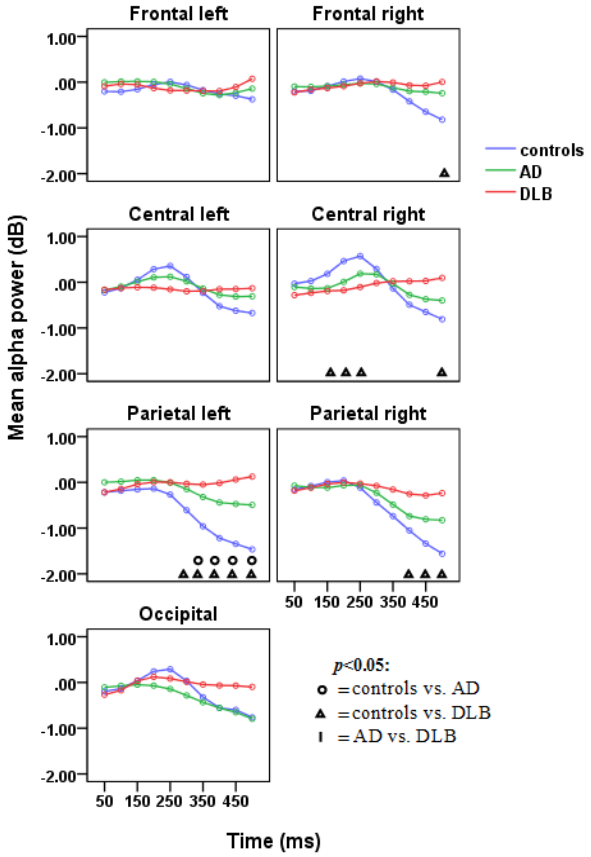


Figure 6.7. Mean alpha power (dB) for the post-neutral cue 500 ms interval across each region, for each group (controls, AD, DLB). The time points at which significant differences (p <0.05) between groups occurred are depicted on the plots (after correcting for multiple comparisons using Bonferroni correction).

Figure 6.7 shows the alpha ERSP calculated using the fixed alpha frequency band, whilst the alpha ERSP calculated using IAF is shown in Figure 6.8. The main effect of time (significant for both the fixed alpha and IAF) is evident from the plots: following the neutral cue onset there was an initial ERS followed by an ERD from approximately 300 ms. The power of the ERS and ERD varied according to region (hence the significant region effect); for both the fixed alpha and IAF the ERS was most apparent in the central regions (bilaterally) and the occipital region, whereas the ERD was greatest in the parietal regions (left and right). The time x region interaction was due to variability across regions regarding the time of the peak ERS, as well as variability in onset time of the ERD.

The region x group interaction was significant for the fixed alpha but not IAF (Table 6.3). When using the fixed alpha band there was greater ERD in the controls in the left

parietal region relative to both the DLB (p <0.01) and AD (p = 0.02) groups, but this was not significant when using IAF. The time x group, and time x region x group, interactions for both the fixed alpha and IAF (Table 6.3) are apparent from Figures 6.7 and 6.8. For the fixed alpha (Figure 6.7) there was less ERD in the DLB group relative to the controls at 500 ms in the right frontal and right central regions, but this ERD difference was most evident bilaterally in the parietal regions (across several successive time points in the latter half of the 500 ms interval). The DLBs also exhibited less ERS relative to controls in the right central region between 150-250 ms. The only difference between the AD group and controls was in the left parietal region; the ADs exhibited less ERD relative to the controls between 300-500 ms. Comparable to the fixed alpha, when using the IAF (Figure 6.8) there was less late ERD in the DLB group relative to the controls in the right central and bilateral parietal regions (although relative to the fixed alpha there were fewer significant time points). The ERS difference between the DLB and control groups in the right central region was no longer significant when using IAF, neither was the late ERD difference in the right frontal region. The differences between AD and controls in the left parietal region evident when using fixed alpha were no longer significant when using IAF, however in the IAF occipital region there was less ERD in the AD group in the initial 50 ms relative to the controls.

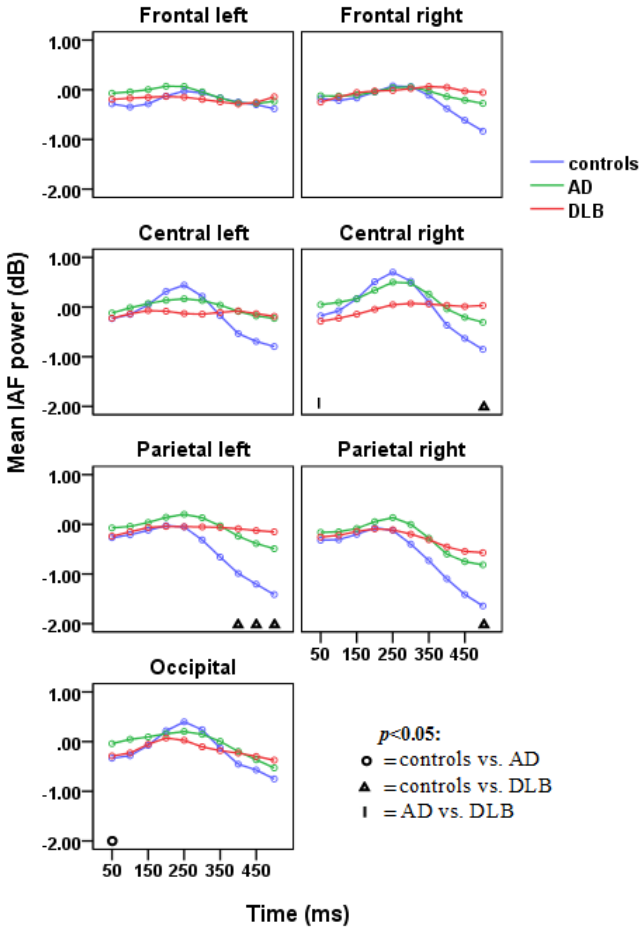


Figure 6.8. Mean IAF power (dB) for the post-neutral cue 500 ms interval across each region, for each group (controls, AD, DLB). The time points at which significant differences (p <0.05) between groups occurred are depicted on the plots (after correcting for multiple comparisons using Bonferroni correction).

Neutral cue beta ERSP

Table 6.3 shows that for the neutral cue beta ERSP there was a main effect of time: across all regions there was an ERD evident from approximately 250 ms. The main effect of group (across all regions, independent of time) was due to less ERD in the DLB group relative to the controls (p <0.01), and there was also a trend for less ERD in the DLB group relative to the AD group (p = 0.07), but there was no difference between the ERD of the controls and AD group (p = 0.38). The significant differences between the groups at each time point (illustrated in Figure 6.9) explains the time x group interaction; there was less ERD in the DLBs relative to the controls, this was evident across all regions in the latter half of the

500 ms, and was fairly consistent with respect to significant time points. The only difference between the AD group and controls was in the left parietel region; there was less ERD in the ADs relative to the controls between 300-500 ms (the ERSP of the two dementia groups was comparable in this region). The DLB group exhibited less ERD relative to both the AD and controls in the right parietal region between 250-350 ms, and in the occipital region between 300-450 ms. However, these group differences across each region must be treated with caution as the the overall group x region interactions were not significant (Table 6.3).

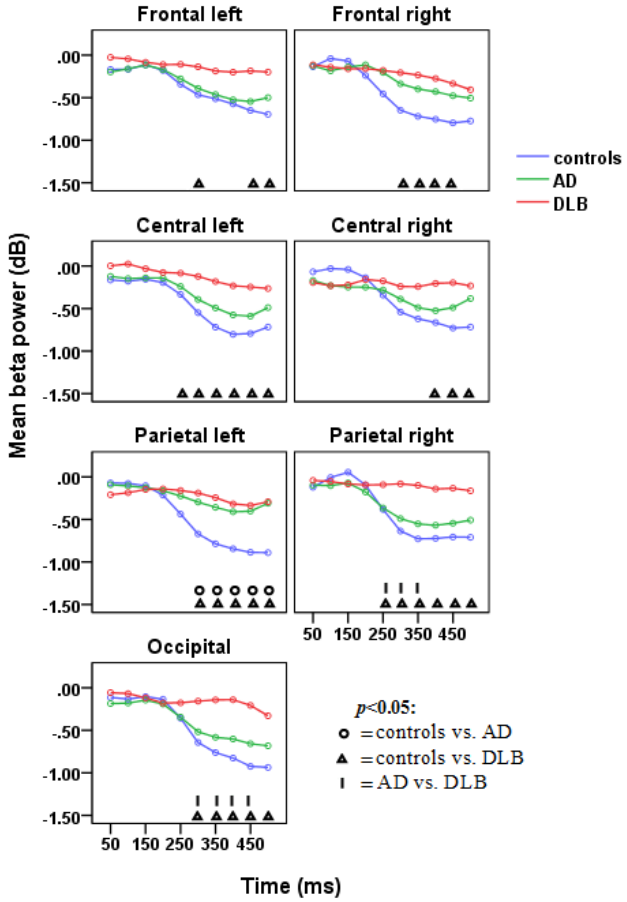


Figure 6.9. Mean beta power (dB) for the post-neutral cue 500 ms interval across each region, for each group (controls, AD, DLB). The time points at which significant differences (p <0.05) between groups occurred are depicted on the plots (after correcting for multiple comparisons using Bonferroni correction).

Neutral cue gamma ERSP

The low gamma (30-45 Hz) power plots are shown in Figure 6.10, and the higher gamma (55-90 Hz) plots are shown in Figure 6.11.

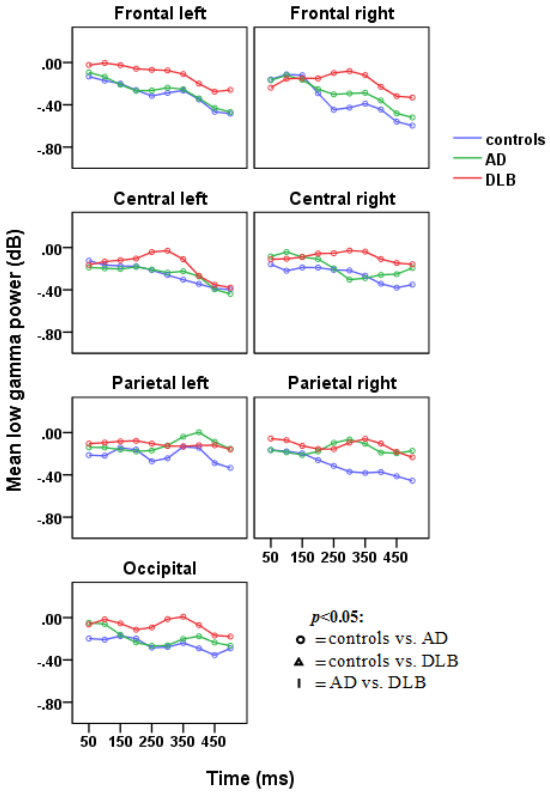


Figure 6.10. Mean low gamma power (dB) for the post-neutral cue 500 ms interval across each region, for each group (controls, AD, DLB).

For the low gamma band there was a significant effect of time (Table 6.3). From Figure 6.10 it is evident that there was much more variability across the time interval in this frequency range relative to the lower frequencies, however the time effect was due to a gradual ERD with increasing time across the 500 ms interval. The power of this ERD was much less than the ERDs evident in the lower frequencies. This ERD was most apparent in the frontal regions, whilst in the right central and occipital regions there seemed to be relatively little ERSP across the time interval, thus explaining the time x region interaction. There was also a main effect of group (Table 6.3); there was less overall ERD (across all regions and times) in the DLB group relative to the controls (p = 0.04), however there was no difference between the ERSP of the DLB and AD groups (p = 0.41), or the controls and AD group (p = 0.79). The results of the post-hoc analyses for each of the individual time points

showed that there were no significant group differences, as expected given the lack of significant group interactions (Table 6.3).

For the 55-90 Hz gamma interval there were significant time, region, and time x region effects (Table 6.3), but no group effects. Figure 6.11 shows that, as with the low gamma range, there was greater variability across the time interval relative to the low frequency ERSPs. The overall time effect is not immediately clear from Figure 6.11, however after averaging the ERSP across all groups and regions (Figure 6.12) it is apparent that across the 500 ms there was a gradual ERD with increasing time, and an ERS which peaked between 300-400 ms. Figure 6.11 shows that the power of the ERD was greater in the central and frontal regions relative to the more posterior regions, hence the significant region effect. The time x region effect is evident from Figure 6.11; the gradual ERD was greatest in the right central region, whilst there was a slight ERS in the occipital region (across all groups) between approximately 250-350 ms.

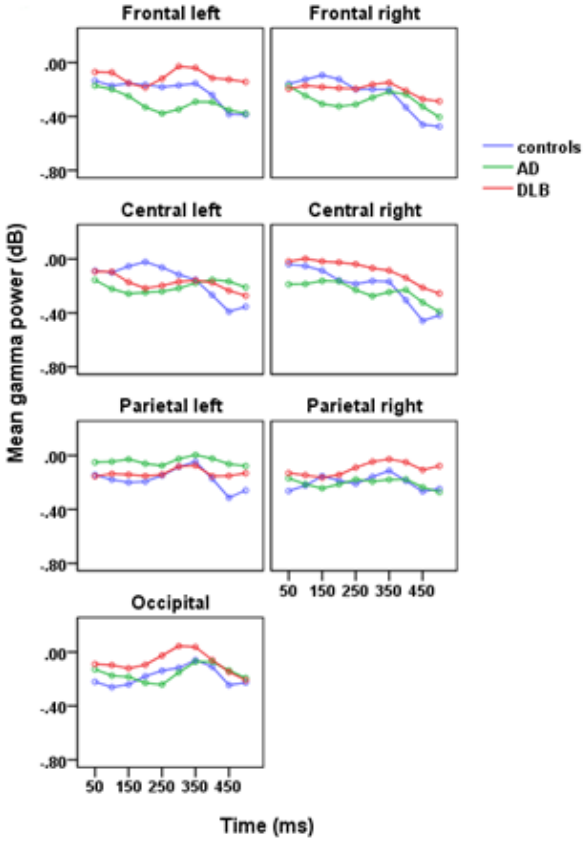


Figure 6.11. Mean gamma power (dB) for the post-neutral cue 500 ms interval across each region, for each group (controls, AD, DLB).

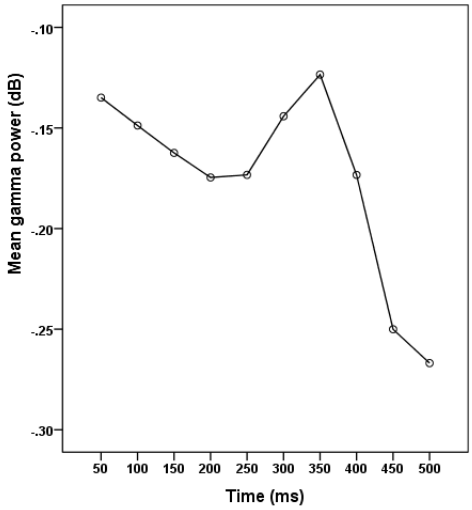


Figure 6.12. Mean gamma power (dB) for the post-neutral cue 500 ms interval, averaged across all regions and all groups.

Neutral cue ERSP summary

- The theta ERSP associated with the presentation of the neutral cue comprised a broad ERS across the 500 ms interval. The DLB showed less ERS relative to the controls, this was significant across the majority of the time points (particularly in the parietal regions). In the left central, right parietal and occipital regions this lack of ERS differentiated the reactivity of the DLB group from both the controls and AD groups.
- In the alpha range, although there were some differences between the fixed alpha and IAF findings, for both methods there was evidence of less ERD after 300 ms in the DLBs relative to the controls in the right central and bilateral parietal regions.
- In the beta range, across all regions there was less ERD in the DLBs in the latter half of the time interval (from approximately 250 ms) relative to the controls.
- In the gamma range (both 30-45 Hz and 55-90 Hz) there was a gradual ERD with increasing time, however there was much more ERSP variability across the time range of interest, and smaller power changes, relative to the lower frequencies. Although in the mean time-frequency plots there appeared to be group differences in this frequency range, overall these differences were not statistically significant. Bursts of gamma activity were more intermittent (in the time and frequency domains) relative to the lower frequencies, potentially explaining the lack of significant group differences (this is discussed further in chapter 8).

6.2.3 Spatial cue

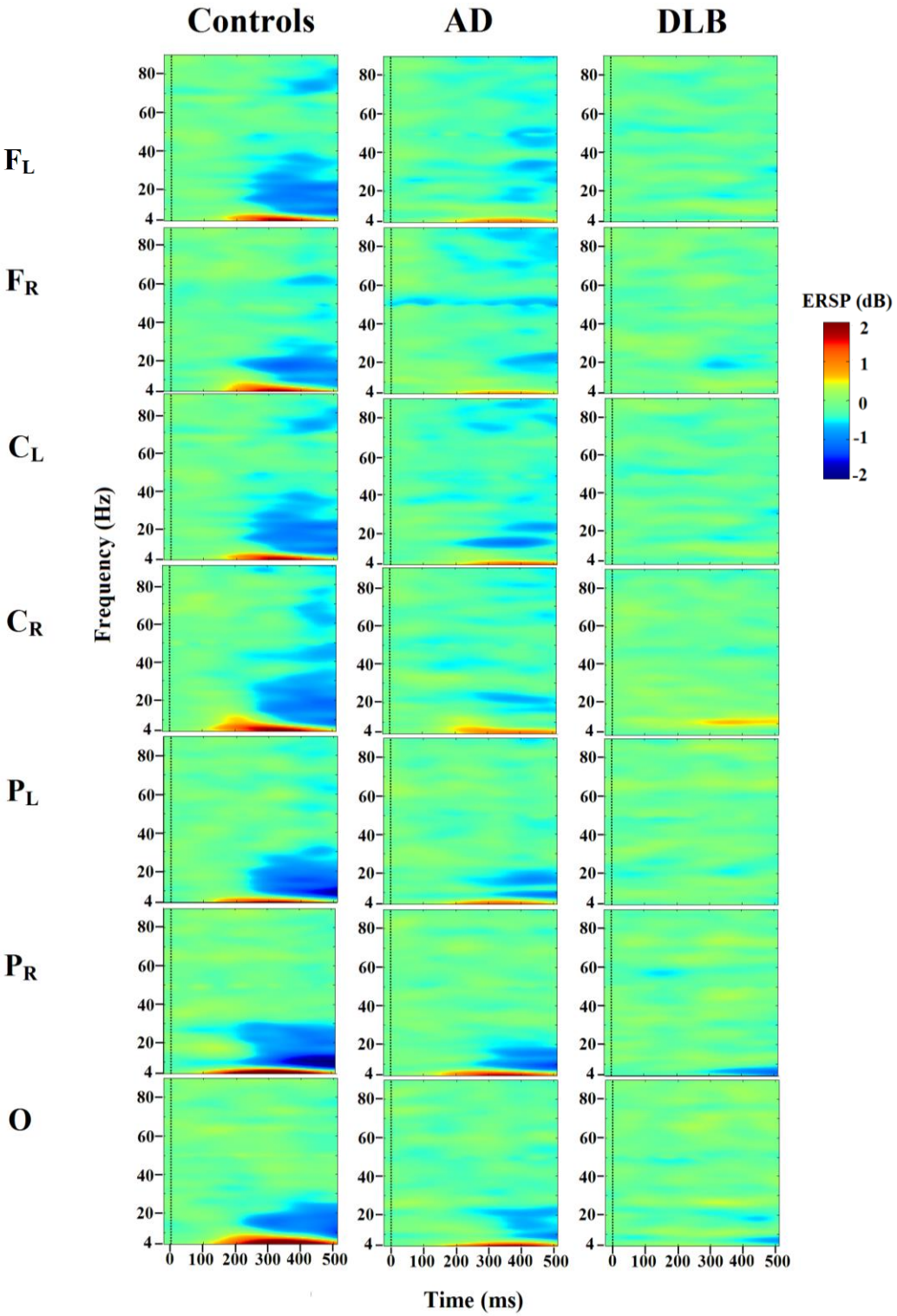


Figure 6.13. Heat maps showing time-frequency ERSP (event-related spectral perturbation) for the spatial cue condition, for each group (controls, AD, DLB), across each region. Power (dB) is plotted in colour (see scale); positive values represent event-related synchronisation, negative values represent event-related desynchronisation. The x axes represent time (ms) post-cue presentation, the vertical line at time 0 ms denotes the onset of the cue. The Y axes represent frequency (Hz) depicted from 4-90 Hz. F_L = Frontal left hemisphere, FR = Frontal right hemisphere, C_L= Central left hemisphere, C_R = Central right hemisphere, P_L = Parietal left hemisphere, P_R = Parietal right hemisphere, O = Occipital region.

Table 6.4. Results of the spatial cue ERSP repeated measures ANOVAs for each frequency band. The ANOVAs were conducted separately for each frequency band, with group (controls, AD, DLB) as the between-subjects factor, and time (10 intervals) and region (7 regions) as within-subject variables. Confidence intervals were adjusted using Bonferroni correction.

	Frequency band					
ANOVA factor	**Theta (4-7 Hz)**	**Alpha (8-14 Hz)**	**IAF (Individual alpha frequency)**	**Beta (14-30 Hz)**	**Low gamma (30-45 Hz)**	**Gamma (55-90 Hz)**
time	$F(1.8, 113.4) = 34.49$, $p < 0.001$**	$F(1.8, 113.6) = 14.61$, $p < 0.001$**	$F(1.7, 107.6) = 13.63$, $p < 0.001$**	$F(2.4, 131.3) = 43.6$, $p < 0.001$**	$F(3.0, 186.9) = 11.45$, $p < 0.001$**	$F(3.1, 190.8) = 11.66$, $p < 0.001$**
region	$F(5.2, 325.3) = 3.96$, $p < 0.001$**	$F(5.2, 319.6) = 11.44$, $p < 0.001$**	$F(5.2, 320.1) = 8.16$, $p < 0.001$**	$F(6, 372) = 1.66$, $p = 0.13$	$F(6, 372) = 4.75$, $p = 0.13$	$F(6, 372) = 4.72$, $p < 0.001$*
time x region	$F(10.6, 659.9) = 3.64$, $p = 0.06$	$F(13.2, 817.4) = 7.46$, $p < 0.001$*	$F(12.7, 784.9) = 7.46$, $p < 0.001$*	$F(14.36, 890.0) = 1.12$, $p < 0.01$*	$F(14.6, 927.4) = 2.02$, $p = 0.01$*	$F(15.8, 979.2) = 3.31$, $p < 0.001$**
group	$F(2, 62) = 11.04$, $p < 0.001$**	$F(2, 62) = 5.40$, $p = 0.01$*	$F(2, 62) = 1.17$, $p = 0.32$	$F(2, 62) = 107.4$, $p < 0.001$**	$F(2, 62) = 2.03$, $p = 0.14$	$F(2, 62) = 3.04$, $p = 0.06$
time x group	$F(3.7, 113.4) = 8.04$, $p < 0.01$*	$F(3.7, 113.6) = 6.46$, $p < 0.001$**	$F(3.5, 107.6) = 3.21$, $p = 0.02$*	$F(4.2, 131.3) = 8.76$, $p < 0.001$**	$F(6.0, 186.9) = 1.66$, $p < 0.001$**	$F(6.2, 190.8) = 2.96$, $p = 0.01$*
region x group	$F(10.5, 325.3) = 2.91$, $p < 0.01$*	$F(10.3, 319.6) = 1.82$, $p = 0.06$	$F(10.3, 320.1) = 1.47$, $p = 0.12$	$F(12, 372) = 1.40$, $p = 0.16$	$F(12, 372) = 1.43$, $p = 0.15$	$F(12, 372) = 0.95$, $p = 0.49$
time x region x group	$F(21.3, 659.9) = 2.46$, $p = 0.07$	$F(26.4, 817.4) = 1.80$, $p = 0.01$*	$F(25.3, 784.9) = 1.58$, $p = 0.04$*	$F(28.7\ 890.0) = 2.14$, $p < 0.01$*	$F(29.9, 927.4) = 1.00$, $p = 0.47$	$F(31.6, 979.2) = 0.81$, $p = 0.77$

* = $p < 0.05$

= statistical trend ($p \leq 0.10$)

Spatial cue plot overview

The time-frequency decompositions for the 500 ms interval following the onset of the spatial cue are depicted in Figure 6.13. In the controls an ERS in the low frequency range (theta/alpha) occurred across all regions, beginning approximately 100 ms post-spatial cue onset in the posterior regions, with a later onset in the more anterior regions. This ERS was apparent in the AD group, however this was not evident in the DLB group. There was however a notable ERS in the DLB group in the right central region in the alpha range between 300-500 ms which was not present in the AD and control groups (the controls instead showed an ERD in the alpha range during this time interval). In the controls, there was an ERD in the beta/low gamma range from approximately 200 ms which was present across all regions. This ERD was present to a lesser extent in the ADs, but appeared to be largely absent in the DLBs, with the exception of ERD activity in the right frontal, right parietal and occipital regions. As with the neutral cue ERSP, in the controls ERDs were evident from approximately 250 ms in the higher gamma range (55-90 Hz) in the central and frontal regions (bilaterally). ERDs were also evident in the higher gamma range in the AD group (although to a lesser extent to the controls); of interest is the ERD evident in the right frontal region between approximately 50-55 Hz across the whole 500 ms interval. In the DLB group there appeared to be an absence of ERDs in the higher gamma range.

Spatial cue theta ERSP

For the spatial cue theta ERSP there was a main effect of time due to an ERS, present across all regions, which peaked at approximately 300-350 ms (Figure 6.14). The main effect of region (Table 6.4) is explicable in terms of greater ERS power in the posterior regions (particularly the right parietal and occipital regions) relative to the more anterior regions. The main effect of group was due to less ERS (across all regions, independent of time) in the DLB group relative to both the controls (p <0.001) and AD groups (p <0.01), whilst there was no difference between controls and AD groups (p = 0.44). The group interactions (Table 6.4) are evident from the significant group differences depicted in Figure 6.14. The only difference between the AD group and controls occurred in the occipital region, with less ERS in the AD group relative to the controls in the 200-400 ms interval. With the exception of the right frontal region, there was less ERS in the DLB group relative to the controls in all regions; in

the right parietal region this ERS difference was significant across all time points from 100 ms post-stimulus. This lack of ERS in the DLB group was significantly less than both the controls and AD group in the right parietal region between 150-500 ms, the occipital region between 350-500 ms, the left central region between 300-400 ms, and in the right central region between 300-450 ms.

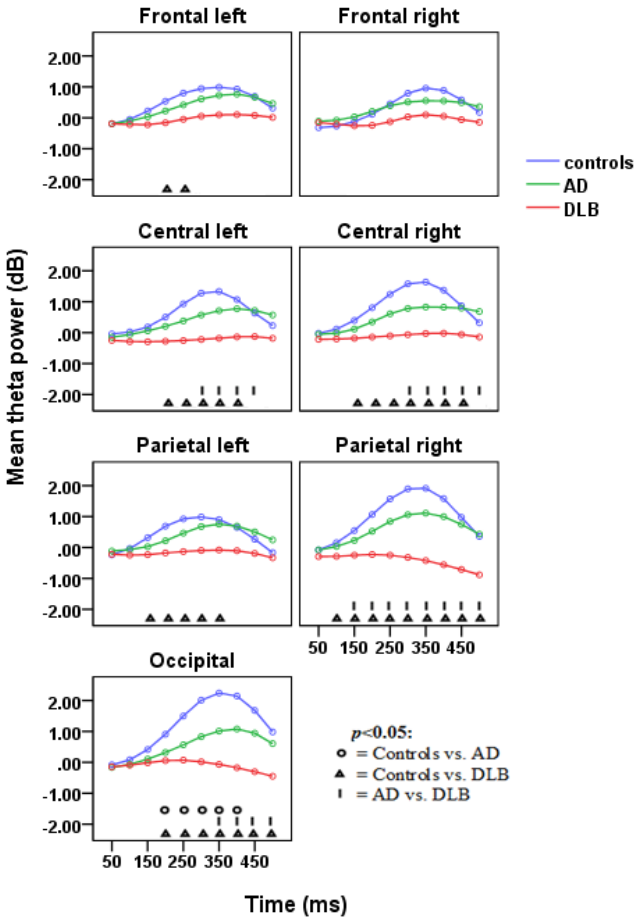


Figure 6.14. Mean theta power (dB) for the post-spatial cue 500 ms interval across each region, for each group (controls, AD, DLB). The time points at which significant differences (p <0.05) between groups occurred are depicted on the plots (after correcting for multiple comparisons using Bonferroni correction).

Spatial cue alpha ERSP

Figure 6.15 depicts the power plots for each region calculated using the fixed alpha frequency band, whilst Figure 6.16 shows the IAF power plots.

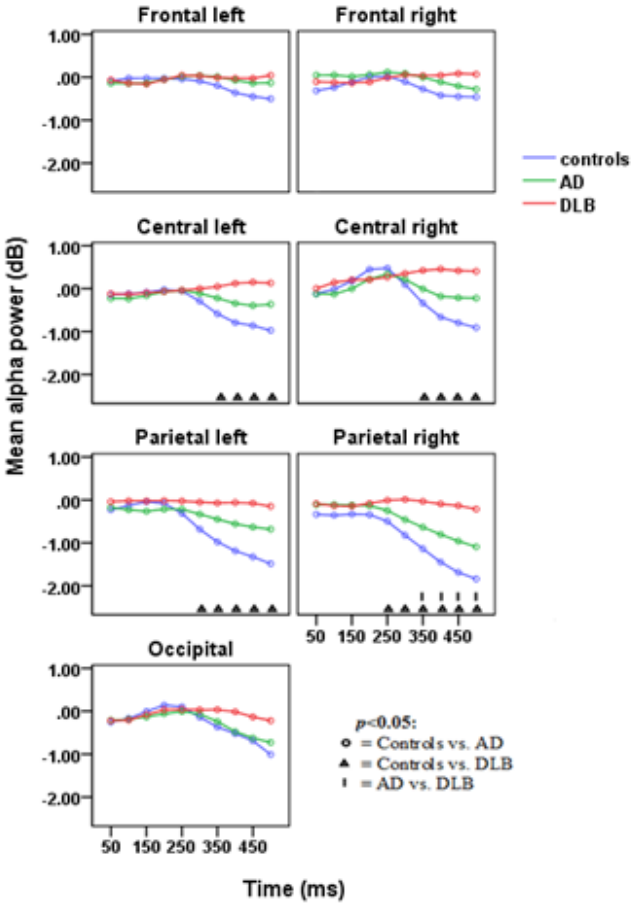


Figure 6.15. Mean alpha power (dB) for the post-spatial cue 500 ms interval across each region, for each group (controls, AD, DLB). The time points at which significant differences (p <0.05) between groups occurred are depicted on the plots (after correcting for multiple comparisons using Bonferroni correction).

Table 6.4 shows that for the alpha ERSP there was a main effect of region (for both the fixed alpha and IAF); as evident in Figures 6.15 and 6.16 the alpha ERSP was greatest in the central and parietal regions bilaterally. The main effect of time (for both the fixed alpha and IAF) was due to an ERD evident from approximately 250 ms. This is ERD was most apparent in the central and parietal regions bilaterally, whilst an early ERS was evident in the right central and occipital regions (particularly when using IAF), thus explaining the time x region interaction.

For the fixed alpha band, the main effect of group was due to diminished ERD in the DLB group relative to the controls (p = 0.01), there was no difference between the DLB and AD groups (p = 0.23), or AD and controls (p = 0.34). When using IAF (Figure 6.16) it is clear that the disparity between groups in the late ERD was less than when using the fixed alpha band (particularly in the parietal regions), therefore explaining the lack of overall group effect

when using IAF (Table 6.4). The group interactions (time x group, time x region x group) are apparent from the group differences depicted in Figures 6.15 and 6.16. For both the fixed alpha and IAF, differences between the groups were evident in the central and parietal regions bilaterally. For the fixed alpha band (Figure 6.15), there was less late ERD in the DLBs relative to the controls in the central and parietal regions bilaterally, and in the right parietal region the DLB ERD was also significantly less than the AD group ERD between 350-500 ms. When using IAF (Figure 6.16) the ERD difference between DLB and controls was no longer significant in the right parietal region, although there was less ERD in the DLBs relative to the controls between 450-500 ms in the left parietal and central (bilateral) regions. For the IAF there was less ERD in the AD group relative to the controls at 100 ms in the right parietal region.

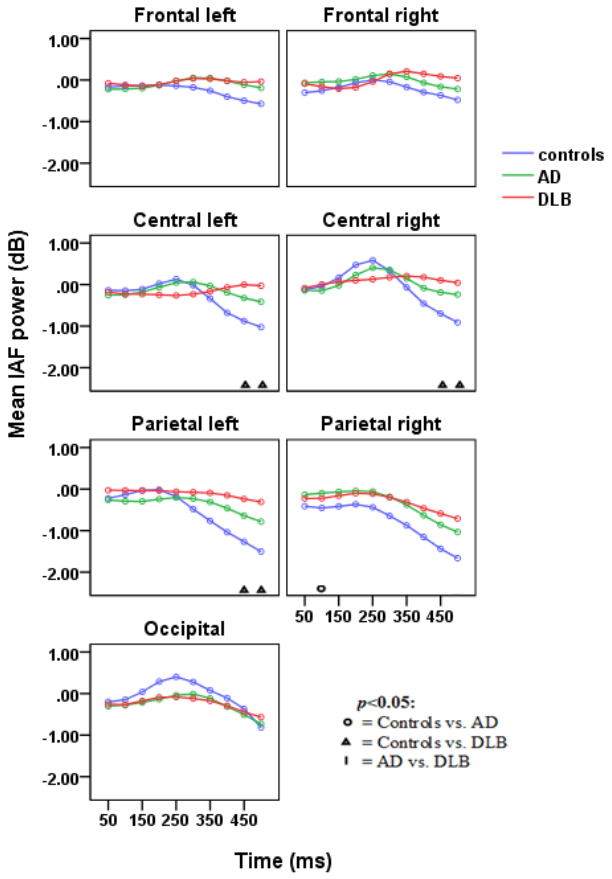


Figure 6.16. Mean IAF (individual alpha power) (dB) for the post-spatial cue 500 ms interval across each region, for each group (controls, AD, DLB). The time points at which significant differences (p <0.05) between groups occurred are depicted on the plots (after correcting for multiple comparisons using Bonferroni correction).

Spatial cue beta ERSP

The main effect of time for the beta ERSP (Table 6.4) was due to an ERD in the latter half of the 500 ms interval (Figure 6.17). This ERD was greatest in the central and parietal regions, hence the time x region interaction. The main effect of group (Table 6.4) is explicable in terms of a lack of ERD in the DLB group relative to the both the controls (p <0.001) and AD group (p = 0.04), there was no difference in the ERD of the controls and AD group (p = 0.20). The group differences shown in Figure 6.17 explain the time x group, and time x region x group interactions. The left parietal region was the only region in which the AD group exhibited less ERD relative to the controls; this occurred between 300-400 ms. There was less ERD in the DLB group relative to the controls in the latter half of the 500 ms interval in the left frontal, left central, bilateral parietal, and occipital regions. In the left central region, this lack of ERD in the DLB group was also less than that of the AD group ERD between 400-450 ms. In the left frontal region both the controls and AD group showed greater early ERD relative to the DLBs between 150-250 ms.

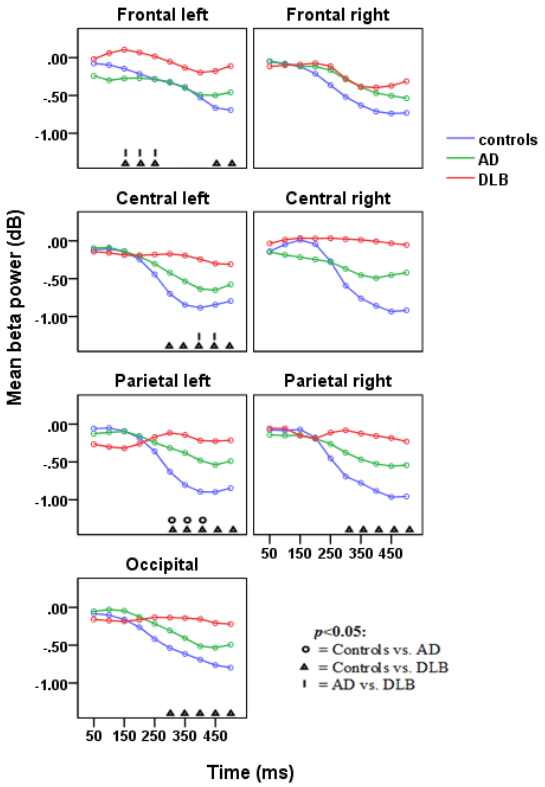


Figure 6.17. Mean beta power (dB) for the post-spatial cue 500 ms interval across each region, for each group (controls, AD, DLB). The time points at which significant differences (p <0.05) between groups occurred are depicted on the plots (after correcting for multiple comparisons using Bonferroni correction).

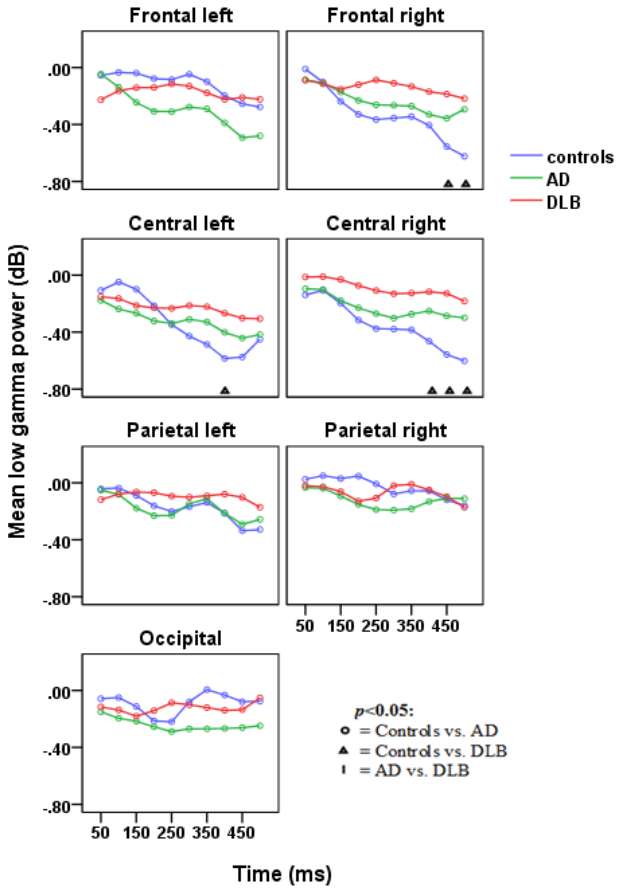


Figure 6.18. Mean low gamma power (dB) for the post-spatial cue 500 ms interval across each region, for each group (controls, AD, DLB). The time points at which significant differences (p <0.05) between groups occurred are depicted on the plots (after correcting for multiple comparisons using Bonferroni correction).

The low gamma power plots are depicted in Figure 6.18, whilst the higher gamma band power plots are shown in Figure 6.19. For the low gamma band there was a main effect of time (Table 6.4), upon viewing Figure 6.18 it is apparent that this was due to a gradual ERD with increasing time. The time x region interaction was due to the ERD being more evident in the frontal and central regions relative to the posterior regions. The time x group interaction was due to less late ERD in the DLB group relative to the controls; post-hoc analyses results showed that this was significant in the right frontal region between 450-500 ms, left central region at 350 ms, and the right central region between 400-500 ms (Figure 6.18).

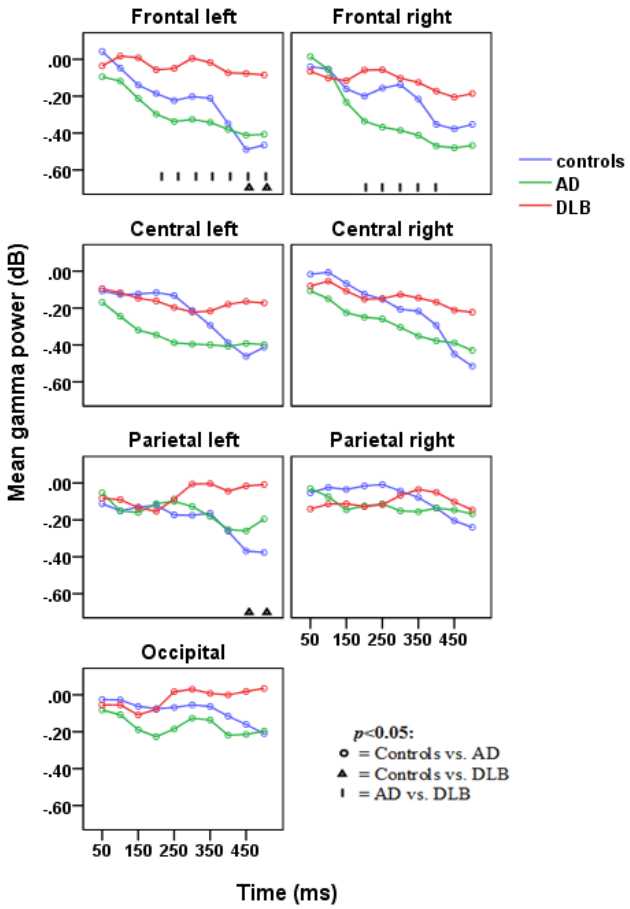


Figure 6.19. Mean gamma power (dB) for the post-spatial cue 500 ms interval across each region, for each group (controls, AD, DLB). The time points at which significant differences (p <0.05) between groups occurred are depicted on the plots (after correcting for multiple comparisons using Bonferroni correction).

In the 55-90 Hz gamma range there was a significant effect of region (Table 6.4), Figure 6.19 shows there was greater ERSP in the frontal and central regions relative to the posterior regions (particularly the right parietal and occipital regions). The trend for an overall group effect (Table 6.4) was due to a trend for reduced ERD (across all times and regions) in the DLB group relative to the AD group (p = 0.05). The main effect of time was due to a gradual ERD with increasing time (Figure 6.19). This ERD was more apparent in the frontal and central regions relative to the posterior regions, which explains the time x region interaction. The significant time x group interaction (Table 6.4) is evident from the group differences depicted in Figure 6.19; there was less ERD in the DLB group relative to the controls which was significant between 450-500 ms in the left frontal and left parietal regions. In the frontal regions there was significantly less ERD in the DLBs relative to the AD group; in the left frontal region this occurred between 200-500 ms, in the right frontal region this was

significant between 200-400 ms. As the group x region interactions were not significant (Table 6.4), the results of these group differences in each region (depicted in Figure 6.19) must be treated with caution.

Spatial cue ERSP summary

- Across each frequency band of interest, the control group spatial cue ERSP was broadly comparable to the neutral cue ERSP.
- In the theta frequency band there was less ERS in the DLBs relative to the controls across the majority of regions. The lack of ERS in the DLBs was also less than that of the AD group at numerous time points in the left central, right central, right parietal and occipital regions. In the occipital region, the ADs showed less ERS relative to controls in the latter time points of the 500 ms interval.
- In the alpha band, the significant group differences were evident in the same regions when using both the fixed alpha band and IAF. A consistent finding when using both methods was less late ERD in the DLB group relative to the controls in the central regions (bilaterally) and in the left parietal region.
- In the beta range there was less ERD in the DLB group relative to the controls in the latter half of the 500 ms interval; this was significant across all regions except the right frontal and right central regions. There was also less ERD in the DLB relative to the AD group at time points in the left frontal and left central region. In the left parietal region, the AD group ERD was significantly less than controls between 300-400 ms.
- For both the low and higher gamma ranges, the time x group interaction was significant, but the group interactions with region were not significant. In the low gamma range there was less ERD in the DLB group relative to the controls in the latter half of the 500 ms interval. In the higher gamma range, the time x group interaction was primarily due to a lack of ERD in the DLB group relative to the AD group in the latter half of the 500 ms interval. For both gamma ranges, there were no differences between the controls and AD group ERSP.

6.3 Target-locked ERSP

6.3.1 Congruent target

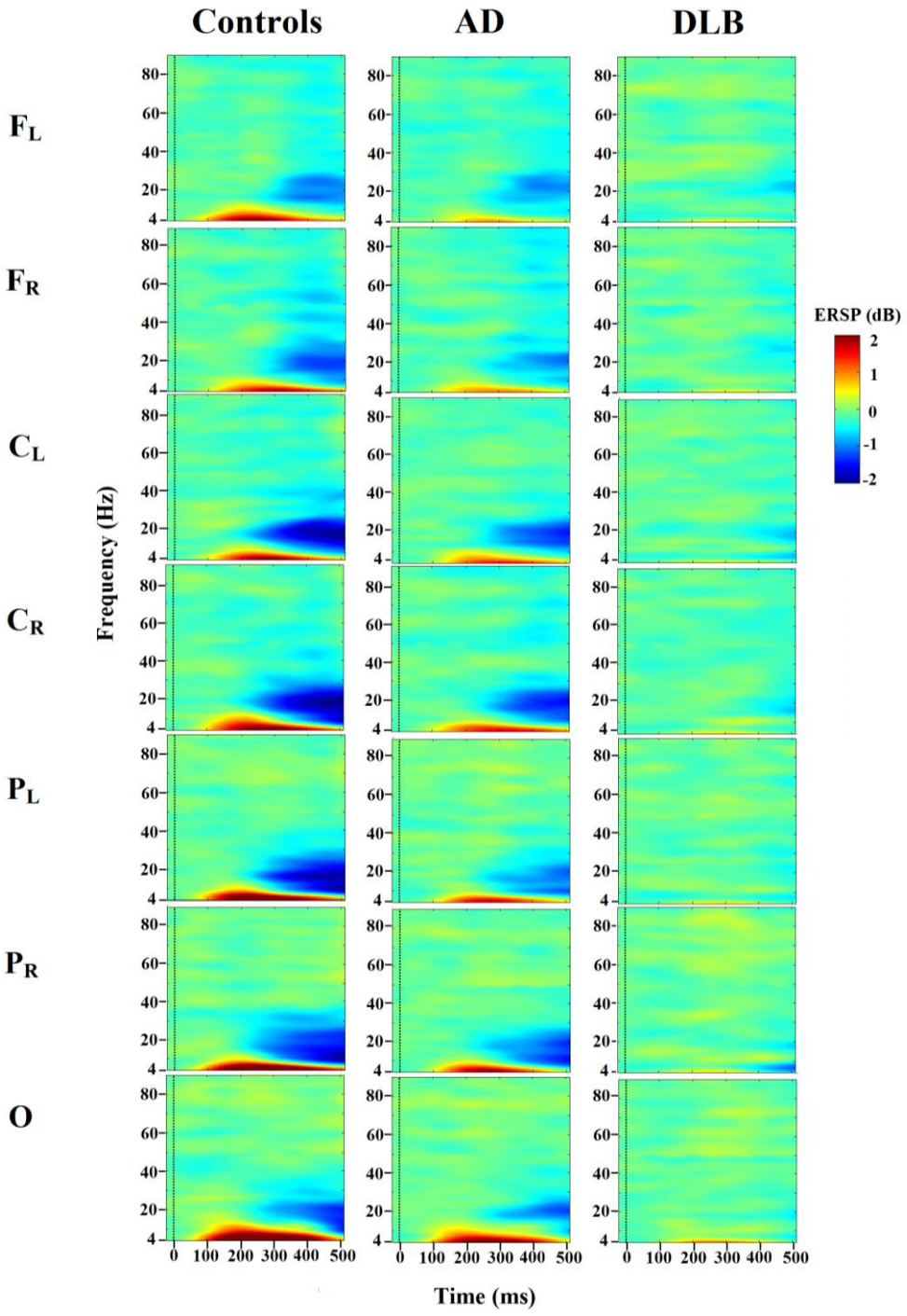


Figure 6.20. Heat maps showing time-frequency ERSP (event-related spectral perturbation) for the congruent target condition, for each group (controls, AD, DLB), across each region. Power (dB) is plotted in colour (see scale); positive values represent event-related synchronisation, negative values represent event-related desynchronisation. The x axes represent time (ms) post-target presentation, the vertical line at time 0 ms denotes the onset of the target. The Y axes represent frequency (Hz) depicted from 4-90 Hz. F_L = Frontal left hemisphere, FR = Frontal right hemisphere, C_L= Central left hemisphere, C_R = Central right hemisphere, P_L = Parietal left hemisphere, P_R = Parietal right hemisphere, O = Occipital region.

Table 6.5. Results of the congruent target ERSP repeated measures ANOVAs for each frequency band. The ANOVAs were conducted separately for each frequency band, with group (controls, AD, DLB) as the between-subjects factor, and time (10 intervals) and region (7 regions) as within-subject variables. Confidence intervals were adjusted using Bonferroni correction.

	Frequency band					
ANOVA factor	**Theta (4-7 Hz)**	**Alpha (8-14 Hz)**	**IAF (Individual alpha frequency)**	**Beta (14-30 Hz)**	**Low gamma (30-45 Hz)**	**Gamma (55-90 Hz)**
time	$F(2.2, 133.5) = 69.19$, $p < 0.001$**	$F(1.8, 111.1) = 35.47$, $p < 0.001$**	$F(1.9,119.5) = 39.66$, $p < 0.001$**	$F(1.4, 88.4) = 87.81$, $p < 0.001$**	$F(2.5,153.2) = 18.44$, $p < 0.001$*	$F(2.4, 149.4) = 3.51$, $p = 0.03$*
region	$F(5.1,137.9) = 11.10$, $p < 0.001$**	$F(6, 372) = 10.64$, $p < 0.001$**	$F(6, 372) = 9.85$, $p < 0.001$*	$F(5.1, 314.4) = 5.33$, $p < 0.001$**	$F(5.0, 312.0) = 0.62$, $p = 0.69$	$F(6, 372) = 11.46$, $p < 0.001$*
time x region	$F(10.8,670.4) = 8.93$, $p < 0.001$*	$F(11.1,688.8) = 8.86$, $p < 0.001$*	$F(10.7,662.3) = 9.40$, $p < 0.001$*	$F(11.8, 7326) = 3.90$, $p < 0.001$*	$F(13.6,840.7) = 2.16$, $p = 0.01$*	$F(13.6, 840.1) = 4.21$, $p < 0.001$*
group	$F(2, 62) = 14.88$, $p < 0.001$**	$F(2, 62) = 0.27$, $p = 0.77$	$F(2, 62) = 1.60$, $p = 0.21$	$F(2, 62) = 10.11$, $p < 0.001$**	$F(2, 62) = 2.91$, $p = 0.06$	$F(2, 62) = 0.59$, $p = 0.56$
time x group	$F(4.3, 133.5) = 7.45$, $p < 0.001$**	$F(1.8, 111.1) = 8.14$, $p < 0.001$**	$F(3.86,119.5) = 6.72$, $p < 0.001$**	$F(2.9, 88.4) = 12.25$, $p < 0.001$**	$F(4.9, 153.2) = 2.54$, $p = 0.03$*	$F(4.8, 149.4) = 0.56$, $p = 0.73$
region x group	$F(10.3,137.9) = 2.43$, $p = 0.01$*	$F(12, 372) = 2.49$, $p < 0.01$*	$F(12, 372) = 1.67$, $p = 0.08$	$F(10.1,314.4) = 2.00$, $p = 0.03$*	$F(10.1,312.0) = 0.99$, $p = 0.45$	$F(12, 372) = 1.62$, $p = 0.10$
time x region x group	$F(21.6,670.4) = 1.67$, $p < 0.03$*	$F(22.2,688.8) = 3.01$, $p < 0.001$*	$F(21.4,662.3) = 2.59$, $p < 0.001$*	$F(23.6, 7326) = 1.88$, $p = 0.01$*	$F(27.1,840.7) = 0.97$, $p = 0.52$	$F(27.1, 840.1) = 0.89$ $p = 0.62$

* = $p < 0.05$

= statistical trend ($p \leq 0.10$)

Congruent target plot overview

As shown in Figure 6.20, in the controls the ERSP associated with the presentation of the congruent target included a low frequency (theta/alpha) ERS which was present across all regions, with an onset of approximately 100 ms post-target (although this varied with region). This ERS was also apparent in the AD group, although to a lesser extent relative to the controls (particularly in the frontal regions), and was largely absent in the DLB group (with the exception of a slight ERS in the occipital region which appeared to be constrained to the theta range). There was ERD in the controls in the latter half of the 500 ms interval, this was primarily in the alpha/beta range in the posterior regions, extending into the gamma range in the central and frontal regions. In the AD group this ERD appeared to be fairly comparable to the controls, whereas ERD in the DLB group was mainly visible in the alpha/beta range (to a much lesser extent relative to both the AD and controls) with a later onset (from approximately 400 ms). Table 6.5 shows that there were significant group interactions for all of the frequency bands of interest with the exception of the 55-90 Hz gamma interval.

Congruent target theta ERSP

The main effect of time in the theta band (Table 6.5) was due to a broad ERS across the 500 ms interval (Figure 6.21), evident in all regions, which peaked at approximately 200-300 ms (slight variability in the peak time across regions explains the significant time x region interaction). The power of the ERS was greatest in the posterior regions, hence the main effect of region (Table 6.5).

The main effect of group was due to less overall ERS in the DLB group relative to the controls (p <0.001) and AD (p = 0.01) groups, there was also a trend for less ERS in the AD group relative to the controls (p = 0.06). The significant group interactions (Table 6.5) are apparent from the significant group differences (at each time point) depicted in Figure 6.21. There was less ERS in the AD group relative to the controls between 150-250 ms in the left frontal and left parietal regions, and between 100-250 ms in the right parietal region. In each region, the DLB group showed reduced ERS compared to the controls across the vast majority of the time points in the 500 ms interval. With the exception of the left frontal region, there were time points in each region at which the lack of ERS in the DLB group was

significantly less than the AD group as well as the controls (the most consecutive time points being in the central (left and right) and occipital regions).

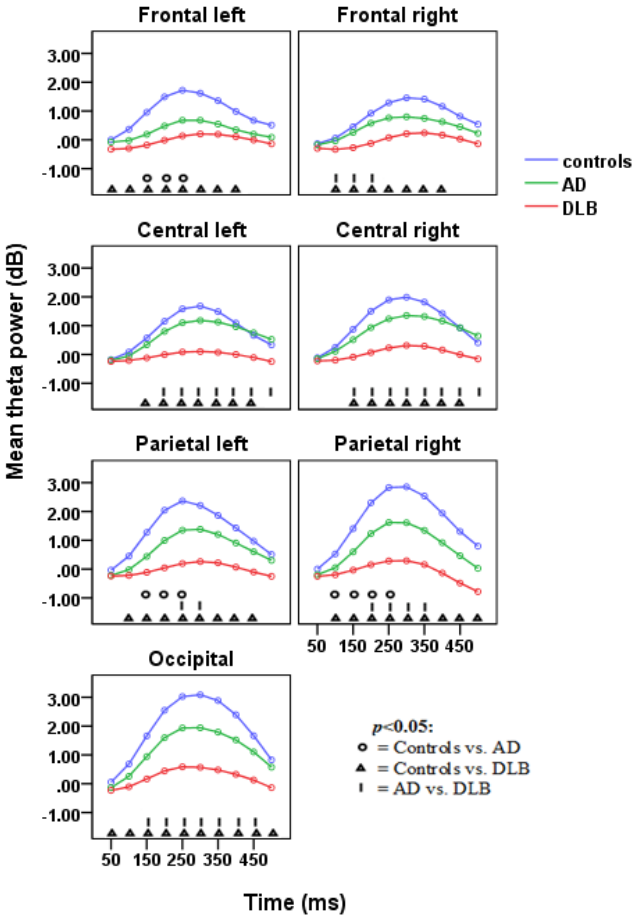


Figure 6.21. Mean theta power (dB) for the post-congruent target 500 ms interval across each region, for each group (controls, AD, DLB). The time points at which significant differences (p <0.05) between groups occurred are depicted on the plots (after correcting for multiple comparisons using Bonferroni correction).

Congruent target alpha ERSP

The congruent alpha ERSP calculated using the fixed alpha band is shown in Figure 6.22, and the IAF ERSP is shown in Figure 6.23. For both the fixed alpha and IAF, the time, region, and time x region effects were significant (Table 6.5). The main effect of region was due to there being greater ERSP in the posterior and central regions relative to the frontal regions. The main effect of time (for both the fixed alpha and IAF) was due to an ERS across

all regions (peaking between 200-250 ms), which was followed by an ERD. There was variability across regions with respect to the onset of the ERD which explains the significant time x region interaction.

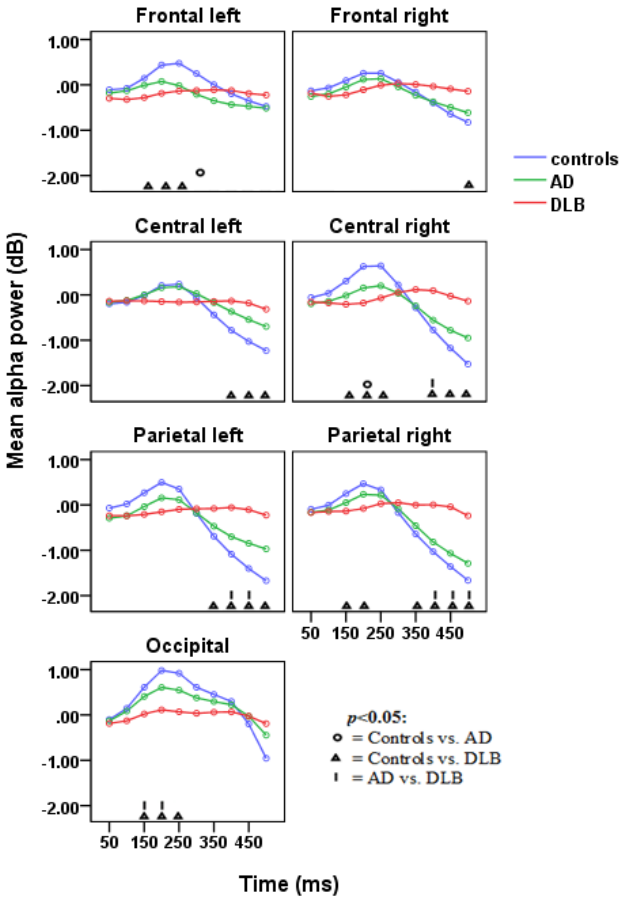


Figure 6.22. Mean alpha power (dB) for the post-congruent target 500 ms interval across each region, for each group (controls, AD, DLB). The time points at which significant differences (p <0.05) between groups occurred are depicted on the plots (after correcting for multiple comparisons using Bonferroni correction).

For both the fixed alpha and IAF there was a significant time x group interaction, whereas the region interactions (region x group, time x region x group) were significant for the fixed alpha band but not the IAF (Table 6.5). When using the fixed alpha there was less ERS in the AD group relative to the controls at 300 ms in the left frontal region and at 200 ms in the right central region. When using the IAF, there was less initial ERS in the AD group relative to the controls in the left parietal region at 100 ms. For the fixed alpha, in each region there were time points at which the ERSP was significantly reduced in the DLB group relative to the controls; the DLBs showed less initial ERS in the left frontal, right central, right parietal and occipital regions, and less ERD at time points in all regions except the left frontal

and occipital regions (Figure 6.22). In the right central and posterior regions, there were time points in which the lack of ERSP in the DLB group was significantly less than both the controls and AD group (Figure 6.22). For the IAF (Figure 6.23), across all regions there were time points at which there was significantly less ERSP in the DLBs relative to the controls, however the time points at which these differences occurred differed to those of the fixed alpha band. With the IAF, there were time points at which there was less early ERS in the DLB group relative to the controls in the right frontal, left central, right parietal and occipital regions. Therefore, although the mean power plots for the fixed alpha and IAF have a relatively similar shape (with comparable ERS and ERD), there was variation between the two methods regarding the time points at which the group differences occurred.

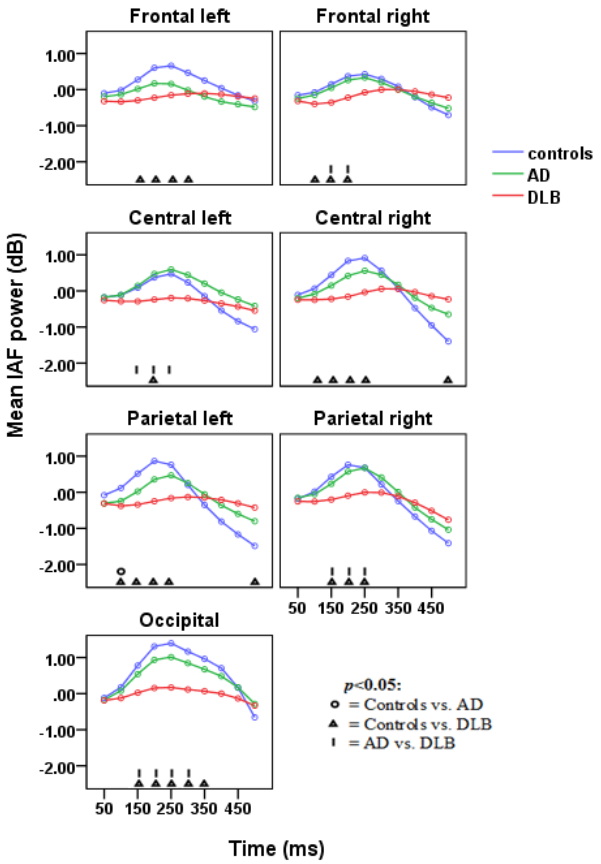


Figure 6.23. Mean IAF power (dB) for the post-congruent target 500 ms interval across each region, for each group (controls, AD, DLB). The time points at which significant differences (p <0.05) between groups occurred are depicted on the plots (after correcting for multiple comparisons using Bonferroni correction).

Congruent target beta ERSP

The main effect of time (Table 6.5) is apparent when referring to Figure 6.24; there was an ERD which was evident across all regions from approximately 200-250 ms, although variability in the onset of this ERD across regions explains the significant time x region effect. There was also a main effect of region (Table 6.5) which was due to the ERD having the greatest power in the central and parietal regions (bilaterally).

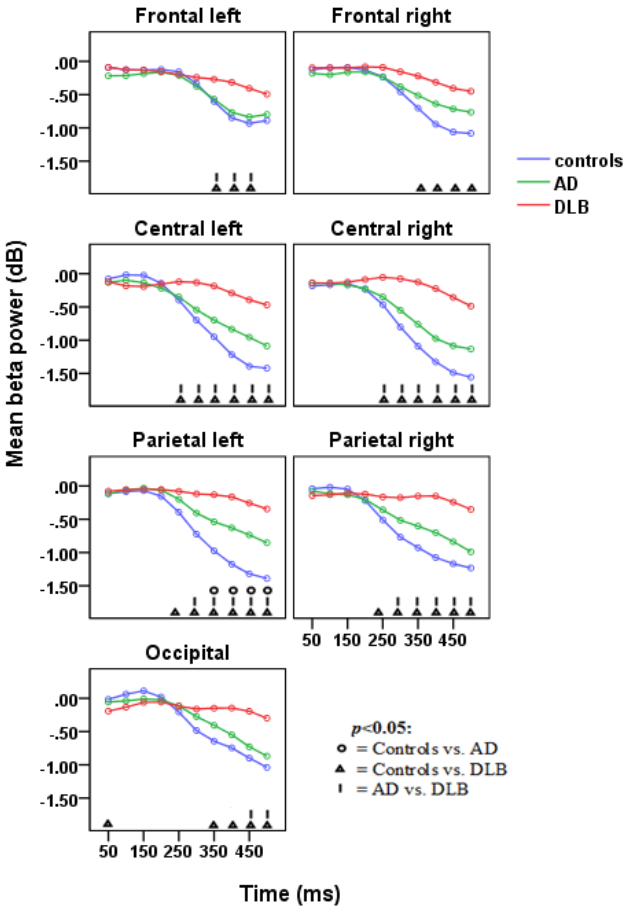


Figure 6.24. Mean beta power (dB) for the post-congruent target 500 ms interval across each region, for each group (controls, AD, DLB). The time points at which significant differences (p <0.05) between groups occurred are depicted on the plots (after correcting for multiple comparisons using Bonferroni correction).

The main effect of group (Table 6.5) was due to less ERD (across all regions, independent of time) in the DLB group relative to the controls (p <0.001) and AD (p = 0.01) groups, there was no difference between the ERD in the controls and AD group (p = 0.37).

The group interactions (Table 6.5) can be explained by the significant group differences depicted in Figure 6.24. The only difference between the ADs and controls was in the left parietal region: between 350-500 ms there was less ERD in the AD group relative to the controls. In all regions there was significantly less ERD in the DLB group compared to the controls at time points in the latter half of the 500 ms interval (Figure 6.24). With the exception of the right frontal region, for the majority of the time points at which the DLB ERD was less than that of the controls, this lack of the ERD in the DLBs was also significantly less than that of the AD group.

Congruent target gamma ERSP

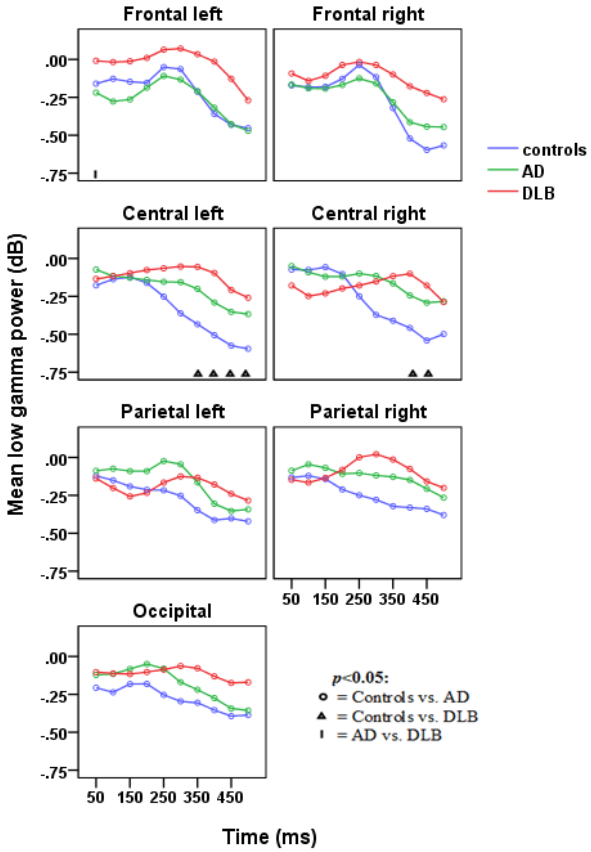


Figure 6.25. Mean low gamma power (dB) for the post-congruent target 500 ms interval across each region, for each group (controls, AD, DLB). The time points at which significant differences (p <0.05) between groups occurred are depicted on the plots (after correcting for multiple comparisons using Bonferroni correction).

In the low gamma band (30-45 Hz) the significant effect of time (Table 6.5) can be seen in Figure 6.25 as an overall gradual ERD with increasing time. There was variation

across regions in the extent to which this ERD was evident, and in some regions there were time intervals at which there was a small ERS (particularly in the frontal regions between approximately 150-300 ms), hence the significant time x region interaction.

Table 6.5 shows that there was a significant time x group interaction (independent of region), Figure 6.26 shows that this was due to group differences in the latter 250 ms in the 500 ms interval. There was less ERD in the DLB group relative to the controls in the latter 250 ms (the DLB group in fact showed an ERS, which peaked at approximately 300-350 ms). This lack of ERD in the DLB group was also significantly less than that of the AD group between 350-500 ms. Between 300-400 ms there was less ERD in the AD group relative to the controls. The trend for an overall group effect (Table 6.5) was due to a trend for less overall ERD (across all times and regions) in the DLB group relative to the controls ($p = 0.06$).

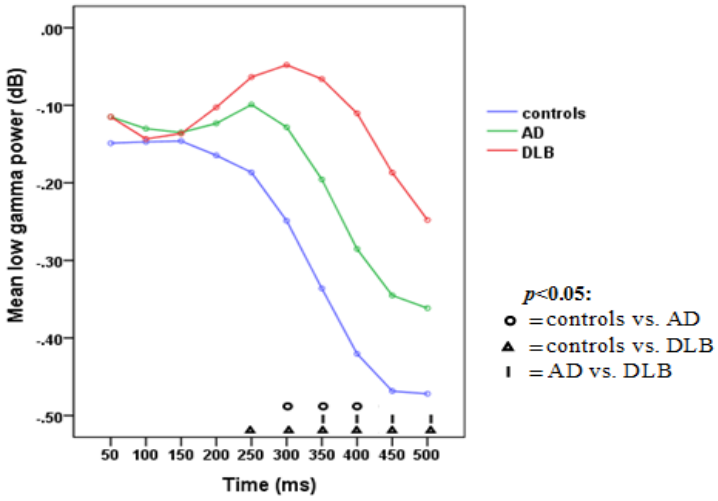


Figure 6.26. Mean low gamma power (dB) for the post-congruent target 500 ms interval, averaged across all regions, for each group. The time points at which significant differences (p <0.05) between groups occurred are depicted on the plots (after correcting for multiple comparisons using Bonferroni correction).

As shown in Table 6.5, in the 55-90 Hz gamma range there was a main effect of time; it can be seen from Figure 6.27 that there was a gradual ERD with increasing time, which was more evident in the frontal and central regions than the posterior regions, thus explaining the significant time x region interaction. The main effect of region (Table 6.5) is explicable in terms of the ERSP across the 500 ms being greater in the frontal regions relative to the more posterior regions.

The overall group effects were not significant, although there was a trend for a region x group interaction (Table 6.5). However, post-hoc analyses showed that there were no significant group differences for any of the regions.

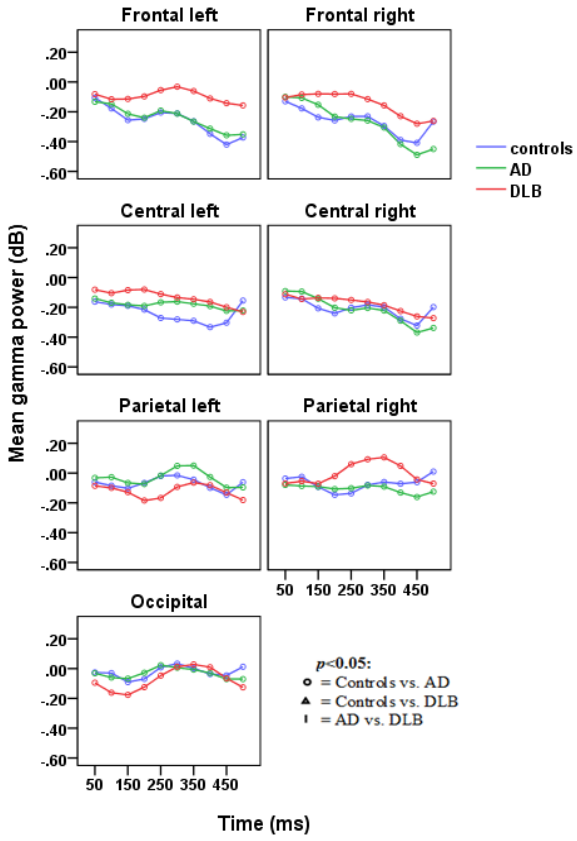


Figure 6.27. Mean gamma power (dB) for the post-congruent target 500 ms interval across each region, for each group (controls, AD, DLB).

Congruent target ERSP summary

- In the theta range the DLB group ERS was less than that of the controls across the majority of the 500 ms interval (in all regions). In several regions, particularly the central (bilateral) and occipital regions, the lack of ERS in the DLB group was significantly less than both the control and AD groups, therefore this lack of theta ERS was characteristic of the DLB group. There was less ERS in the AD group relative to the controls in the first half of the 500 ms interval in the left frontal and parietal (bilateral) regions.
- In the alpha range, the congruent ERSP comprised an initial ERS followed by an ERD in the latter half of the 500 ms interval. For both the fixed alpha and IAF there were time points in each region at which the DLB group exhibited less alpha reactivity than the controls. Although there were differences between the fixed alpha and IAF regarding the group differences, a consistency between the two techniques was reduced ERS in the DLB group relative to the controls and AD group in the occipital region.
- Beta range ERD, which was evident across all regions from approximately 200-250 ms, was significantly less in the DLB group relative to both the AD and controls, particularly in the central and parietal regions bilaterally. In the left parietal region, this ERD was less in the AD group relative to the controls.
- In the gamma range, the ERSP was more variable (and of a lower power) across the 500 ms interval relative to the lower frequencies, however there appeared to be a gradual ERD with increasing time in the frontal and central regions. In the low gamma range (across all regions) there were group differences in the latter half of the 500 ms interval; primarily due to a lack of ERD in the DLB group.

6.3.2 Incongruent target

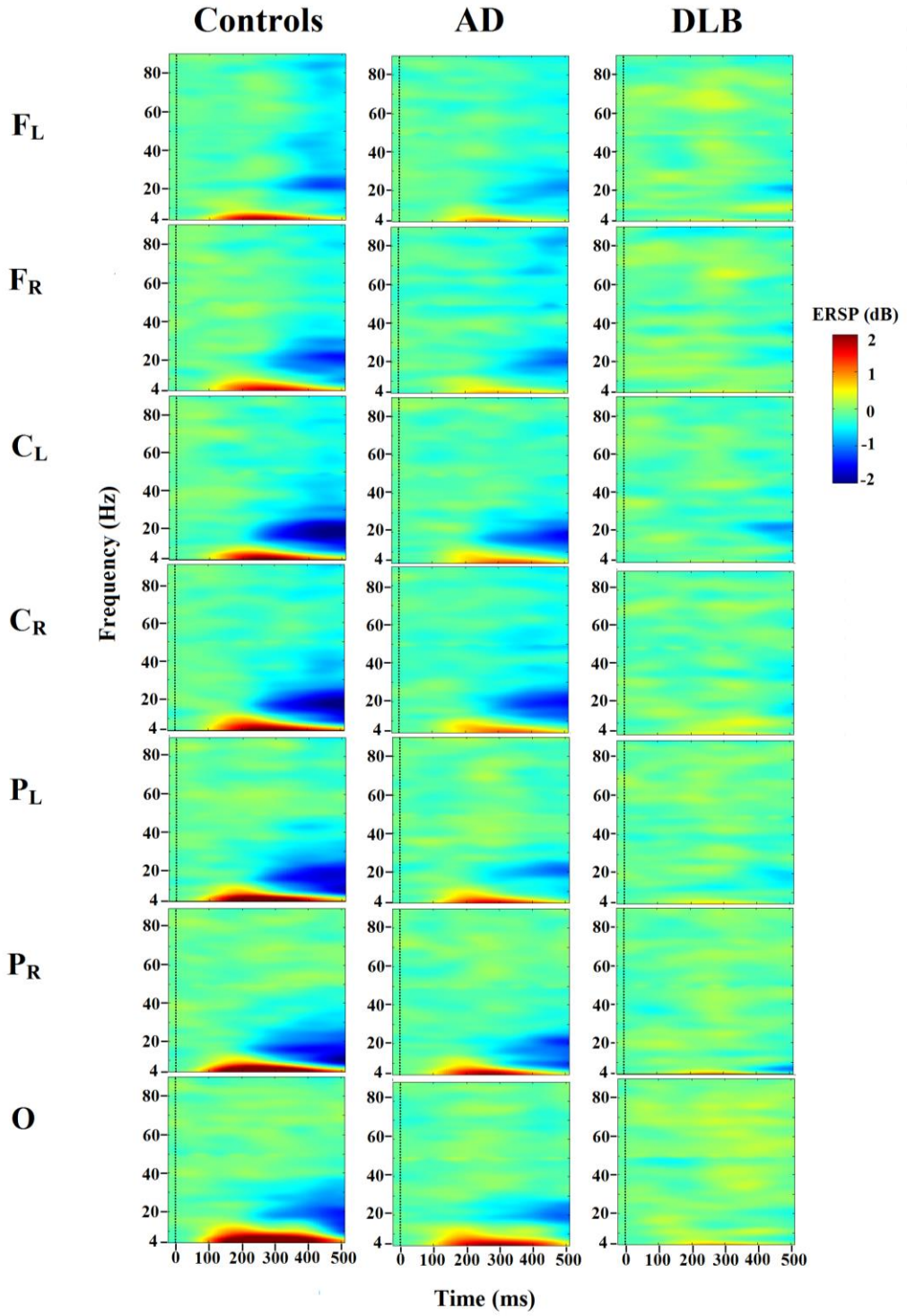


Figure 6.28. Heat maps showing time-frequency ERSP (event-related spectral perturbation) for the incongruent target condition, for each group (controls, AD, DLB), across each region. Power (dB) is plotted in colour (see scale); positive values represent event-related synchronisation, negative values represent event-related desynchronisation. The x axes represent time (ms) post-target presentation, the vertical line at time 0 ms denotes the onset of the target. The Y axes represent frequency (Hz) depicted from 4-90 Hz. F_L = Frontal left hemisphere, FR = Frontal right hemisphere, C_L= Central left hemisphere, C_R = Central right hemisphere, P_L = Parietal left hemisphere, P_R = Parietal right hemisphere, O = Occipital region.

Table 6.6. Results of the incongruent target ERSP repeated measures ANOVAs for each frequency band. The ANOVAs were conducted separately for each frequency band, with group (controls, AD, DLB) as the between-subjects factor, and time (10 intervals) and region (7 regions) as within-subject variables. Confidence intervals were adjusted using Bonferroni correction.

	Frequency band					
ANOVA factor	**Theta (4-7 Hz)**	**Alpha (8-14 Hz)**	**IAF (Individual alpha frequency)**	**Beta (14-30 Hz)**	**Low gamma (30-45 Hz)**	**Gamma (55-90 Hz)**
time	$F(2.0, 126.0) = 67.13$, $p < 0.001$**	$F(1.8, 109.7) = 28.74$, $p < 0.001$**	$F(1.8,109.4) = 34.31$, $p < 0.001$**	$F(1.7, 105.4) = 85.37$, $p < 0.001$**	$F(2.2, 138.5) = 21.43$, $p < 0.001$**	$F(2.0,122.8) = 9.04$, $p < 0.001$**
region	$F(6, 372) = 11.68$, $p < 0.001$**	$F(6, 372) = 9.77$, $p < 0.001$**	$F(6, 372) = 7.00$, $p < 0.001$**	$F(4.9,305.1) = 6.94$, $p < 0.001$**	$F(5.1, 318.0) = 2.96$, $p = 0.01$*	$F(6, 372) = 6.99$, $p < .0.001$**
time x region	$F(10.5, 651.1) = 8.61$, $p < 0.001$**	$F(11.4, 703.9) = 9.54$, $p < 0.001$**	$F(10.7, 665.5) = 10.06$, $p < 0.001$**	$F(11.7,724.3) = 4.14$, $p < 0.001$**	$F(14.3, 888.3) = 2.80$, $p < 0.001$**	$F(11.9, 737.5) = 5.18$ $p < 0.001$**
group	$F(2, 62) = 14.71$, $p < 0.001$**	$F(2, 62) = 0.44$, $p = 0.65$	$F(2, 62) = 0.54$, $p = 0.58$	$F(2, 62) = 16.10$, $p < 0.001$**	$F(2, 62) = 2.90$, $p = 0.06$	$F(2, 62) = 1.78$, $p = 0.18$
time x group	$F(4.1, 126.0) = 9.45$, $p < 0.001$**	$F(3.5, 109.7) = 8.74$, $p < 0.001$**	$F(3.5,109.4) = 5.22$, $p < 0.001$**	$F(3.4, 105.4) = 10.15$, $p < 0.001$**	$F(4.5, 138.5) = 6.36$, $p < 0.001$**	$F(4.0,122.8) = 1.15$, $p < 0.001$**
region x group	$F(12, 372) = 2.29$, $p = 0.01$*	$F(6, 372) = 2.23$, $p = 0.01$*	$F(12, 372) = 1.66$, $p = 0.07$	$F(9.8,305.1) = 1.62$ $p = 0.10$	$F(10.3, 318.0) = 0.50$, $p = 0.89$	$F(12, 372) = 1.12$, $p = 0.35$
time x region x group	$F(21.0, 651.1) = 1.09$, $p = 0.35$	$F(22.7, 703.9) = 2.52$, $p < 0.001$**	$F(21.5, 665.5) = 10.06$, $p < 0.001$**	$F(23.4,724.3) = 1.81$, $p = 0.01$*	$F(28.7, 888.3) = 1.09$, $p = 0.34$	$F(23.8, 737.5) = 1.15$ $p = 0.28$

* = $p < 0.05$

= statistical trend ($p \leq 0.10$)

Incongruent target plot overview

The ERSP associated with the presentation of the incongruent target, shown in Figure 6.28, appeared to be fairly comparable to the congruent target ERSP. In the controls there was an ERS across all regions in the theta/alpha range, which had an onset of approximately 100 ms. As with the congruent target, this ERS was apparent to a lesser extent in the AD group, yet appeared to be largely absent in the DLB group. In the controls ERD was evident from approximately 300 ms in the alpha/beta/low gamma range across all regions, extending into the higher gamma range in the frontal and central regions. In the AD group this ERD seemed to be broadly comparable to the controls, however there appeared to be more gamma ERD in the right frontal region relative to the controls, whilst in the left frontal region the gamma ERD was greater in the controls than the AD group. In the DLB group this ERD was only present between 400-500 ms in the lower frequencies (alpha/beta), mainly in the left frontal, left central and parietal regions. The gamma ERD evident in the frontal and central regions in the controls and AD group was absent in the DLBs; instead the DLB group appeared to show gamma ERS in the frontal regions.

Incongruent target theta ERSP

The significant effect of time (Table 6.6) was due to a broad ERS across the 500 ms, which was evident across all regions, peaking at approximately 250-300 ms (Figure 6.29). Variability across the regions regarding the time at which the ERS peaked explains the time x region interaction. The power of the ERS was greater in the posterior regions relative to the more anterior regions, and this explained the main effect of region.

The main effect of group (Table 6.6) was due to the mean ERS (across all regions and time points) being greater in the controls relative to the DLB (p <0.001) and AD (p = 0.02) groups, and greater in the AD group relative to the DLB group (p = 0.02). The group interactions (time x group, region x group) are apparent from the significant group differences depicted in Figure 6.29. Compared to the congruent theta, there were more regions in which the AD ERS was significantly less than that of the controls; with the exception of the left frontal region, there were several successive time points in each region in which this difference was significant. Across each of the regions, the DLB group ERS was significantly less than that of the controls across the vast majority of the 500 ms interval (comparable to the

congruent theta ERSP). In the left central, right parietal and occipital regions there were time points at which this diminished ERS in the DLB group was also significantly less than the AD group (in addition to the controls).

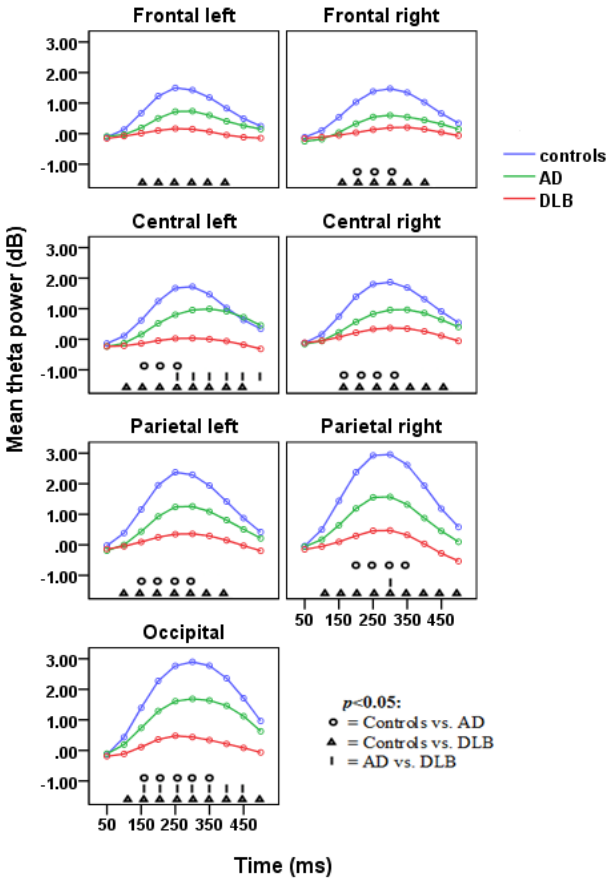


Figure 6.29. Mean theta power (dB) for the post-incongruent target 500 ms interval across each region, for each group (controls, AD, DLB). The time points at which significant differences (p <0.05) between groups occurred are depicted on the plots (after correcting for multiple comparisons using Bonferroni correction).

Incongruent target alpha ERSP

The fixed alpha power plots are depicted in Figure 6.30, and the IAF plots are shown in Figure 6.31.

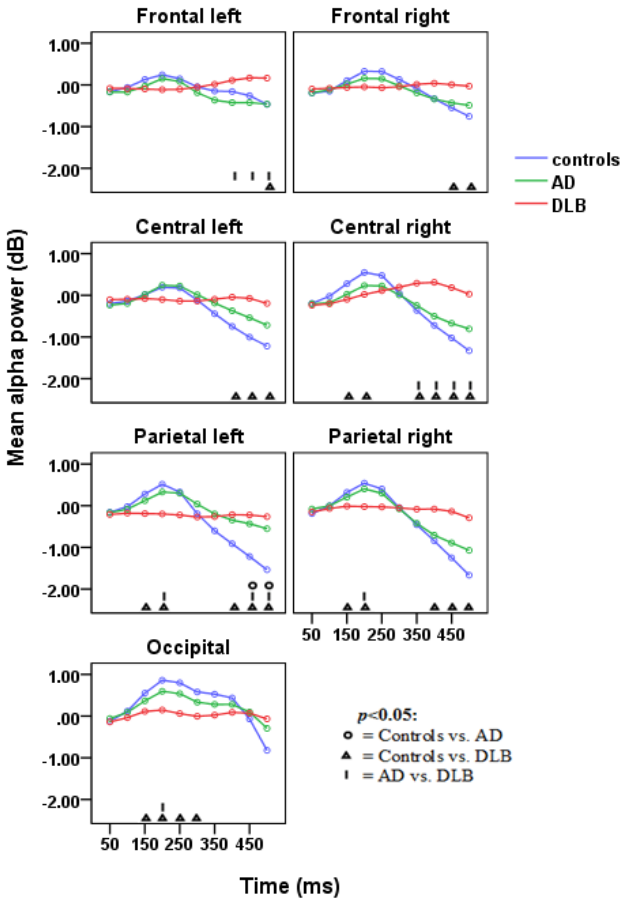


Figure 6.30. Mean alpha power (dB) for the post-incongruent target 500 ms interval across each region, for each group (controls, AD, DLB). The time points at which significant differences (p <0.05) between groups occurred are depicted on the plots (after correcting for multiple comparisons using Bonferroni correction).

Table 6.6 shows that for both the fixed alpha and the IAF there were significant time, region, and time x region interactions. As with the congruent target alpha ERSP, the main effect of time was due an early ERS (peaking at approximately 200-250 ms), which was followed by an ERD in the latter half of the 500 ms (in all regions). Variability in the peak time of the ERS, and the onset time of the ERD, explains the time x region interaction. In the occipital region, the ERS (when calculated using the fixed alpha and IAF) was evident across a much broader time interval relative to the other regions. The region effect was due to there being less ERSP in the frontal regions relative to the other regions (for both the fixed alpha and IAF).

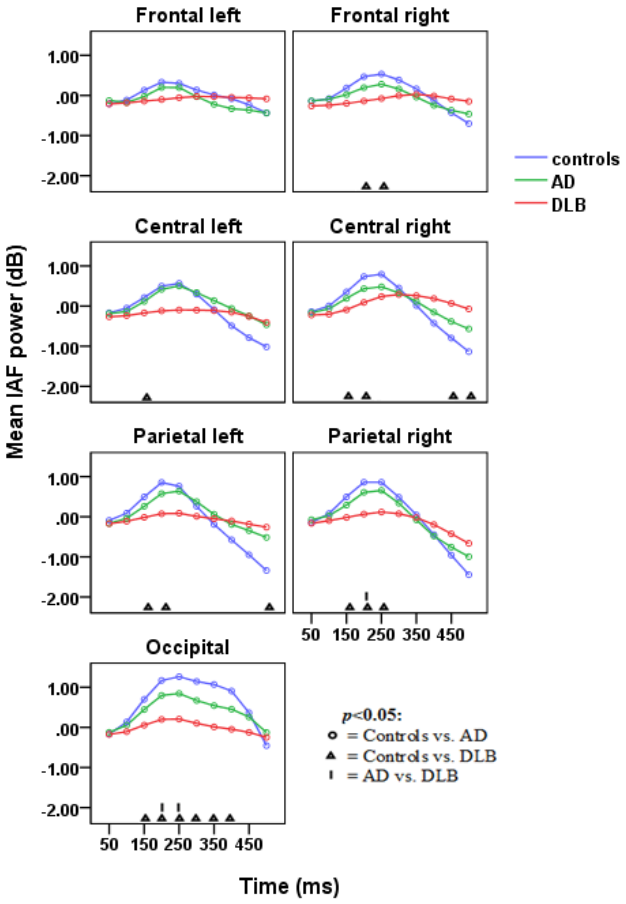


Figure 6.31. Mean IAF power (dB) for the post-incongruent target 500 ms interval across each region, for each group (controls, AD, DLB). The time points at which significant differences (p <0.05) between groups occurred are depicted on the plots (after correcting for multiple comparisons using Bonferroni correction).

For both the fixed alpha and IAF, there were significant time x group, and time x region x group effects, however the region x group effect was only significant for the fixed alpha (although there was a trend when using IAF) (Table 6.6). Figure 6.30 shows that when using the fixed alpha band the only significant difference between the AD and control ERSP was in the left parietal region: less ERD in the AD group compared to the controls between 450-500 ms. When using the IAF, this difference between the AD and control groups was no longer significant (Figure 6.31). For the fixed alpha there were time points across all regions at which there was less ERSP in the DLB group relative to the controls (less ERS and ERD, this varied according to region). When using the IAF, reduced ERSP in the DLBs relative to the controls was evident in all regions except the left frontal region; this primarily comprised less early ERS in the DLB group compared to the controls. In the right central region, for both the fixed alpha and IAF, it seems that the significant group differences were due to an apparent ERS slowing (in the time domain) in the DLB group relative to the controls and AD

group. Figure 6.30 shows that for the fixed alpha there were time points in the majority of the regions at which the reduced ERSP in the DLB group was significantly less than both the controls and AD groups. For the IAF (Figure 6.31) there were time points at which there was less ERS in the DLB group relative to both the controls and AD group in the right parietal and occipital regions only. Despite there being fewer group differences when using the IAF (relative to the fixed alpha), a consistency between the findings when using the two methods was less ERS in the DLB group compared to both the controls and AD groups at 200 ms in the right parietal and occipital regions. This is indicative of this aberrant alpha activity in the DLB group being a robust finding (as it is evident irrespective of the alpha band method used).

Incongruent target beta ERSP

The main effect of time in the beta range (Table 6.6) was due to an ERD across all regions in the latter 250 ms (comparable to the beta ERD following the presentation of the congruent target). The time x region effect was due to variability in the onset time of this ERD with respect to region (Figure 6.32). The main effect of region is explicable in terms of the power of the ERD being greatest in the central and parietal regions (bilaterally).

The significant group effect (Table 6.6) is evident from Figure 6.32; across all regions (independent of time) there was a lack of ERD in the DLB group relative to both the controls (p <0.001) and AD groups (p <0.01), there was no difference between the ERD of the AD group and controls (p = 0.24). The group interactions (time x group, time x region x group) are apparent from the significant group differences depicted in Figure 6.32. The DLBs exhibited less ERD relative to the controls across all regions in the latter half of the 500 ms interval, with this difference being significant from as early as 150 ms in the right parietal region. In each region, this lack of ERD in the DLB group was significantly less that of both the controls and AD group, particularly in the right hemisphere. In the parietal regions, the AD group ERD was significantly less than that of the controls between 300-500 ms in the left parietal region, and at 350 ms in the right parietal region.

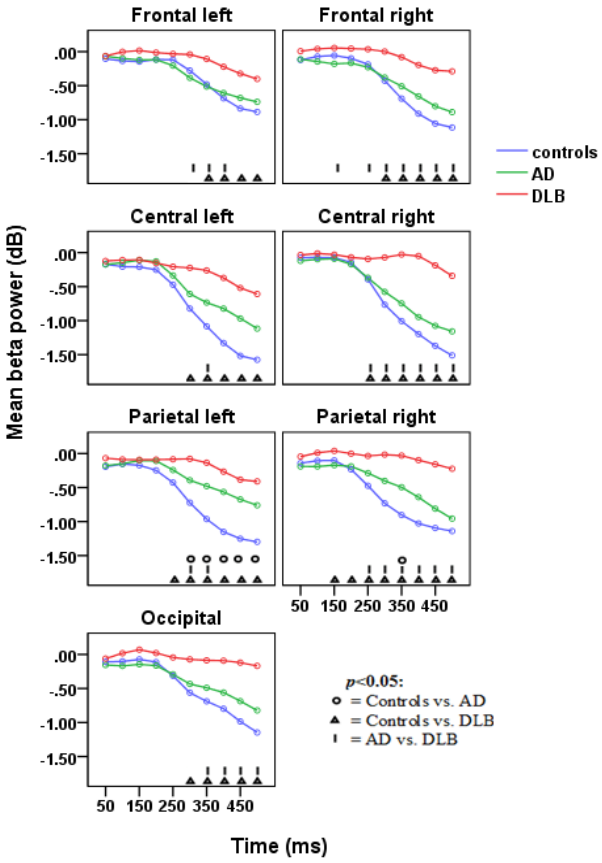


Figure 6.32. Mean beta power (dB) for the post-incongruent target 500 ms interval across each region, for each group (controls, AD, DLB). The time points at which significant differences (p <0.05) between groups occurred are depicted on the plots (after correcting for multiple comparisons using Bonferroni correction).

Incongruent target gamma ERSP

In the low gamma (30-45 Hz) range, the main effect of time (Table 6.6) can be seen from Figure 6.33 as a slight ERD with increasing time. There was variability across the regions regarding the time of the peak ERD, hence the significant time x region interaction. The ERD appeared to be greatest in the frontal and central regions, thus explaining the significant region effect.

Table 6.6 shows that in the low gamma range there was a trend for an overall group effect; this was due to a trend for less ERD in the DLB group compared to the controls (p = 0.06). The time x group interaction, independent of region, is apparent from Figure 6.34; in the 300-500 ms interval the ERD in the controls was greater than that of both the dementia groups, and the lack of ERD in the DLB group was also less than that of the AD group (with the DLB group exhibiting ERS as opposed to ERD in this interval).

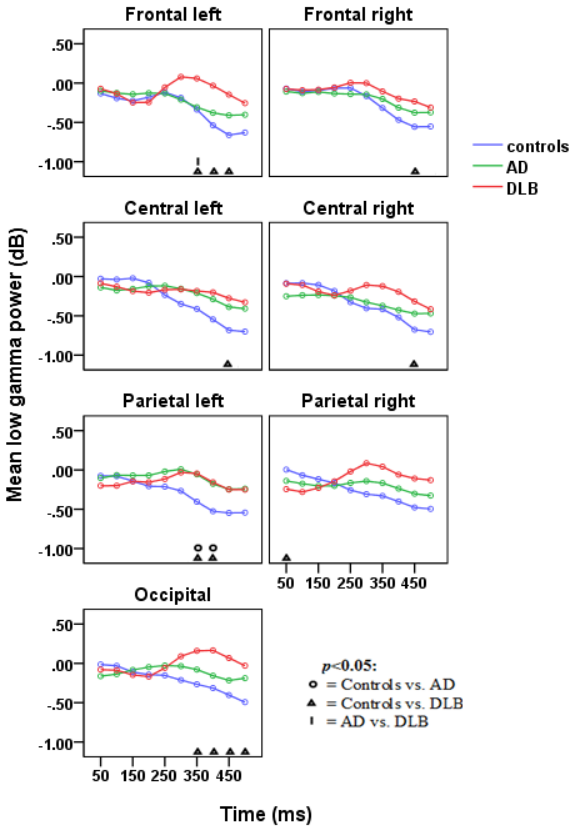


Figure 6.33. Mean low gamma power (dB) for the post-incongruent target 500 ms interval across each region, for each group (controls, AD, DLB). The time points at which significant differences (p <0.05) between groups occurred are depicted on the plots (after correcting for multiple comparisons using Bonferroni correction).

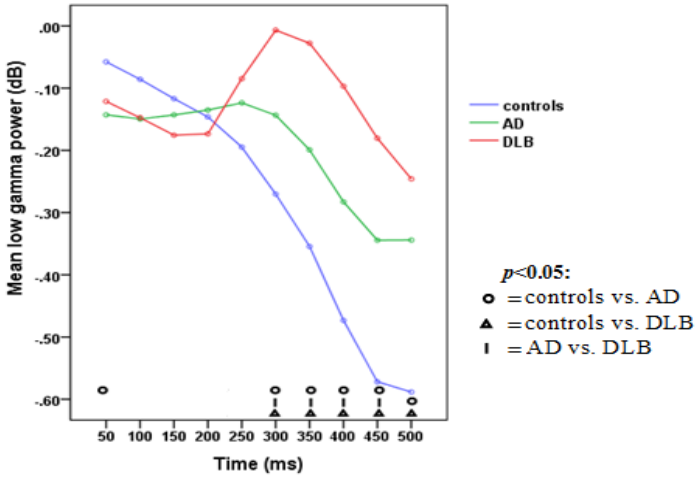


Figure 6.34. Mean low gamma power (dB) for the post-incongruent target 500 ms interval, averaged across all regions, for each group. The time points at which significant differences (p <0.05) between groups occurred are depicted on the plots (after correcting for multiple comparisons using Bonferroni correction).

For the 55-90 Hz gamma interval the significant effect of time (Table 6.6) is evident in Figure 6.35 as a gradual ERD with increasing time (comparable to the low gamma in interval). This ERD is most apparent in the frontal and central regions, and this explains the main effect of region (Table 6.6). The time x region interaction is explicable in terms of the lack of ERD in the latter half of the time interval in the posterior regions relative to the more anterior regions.

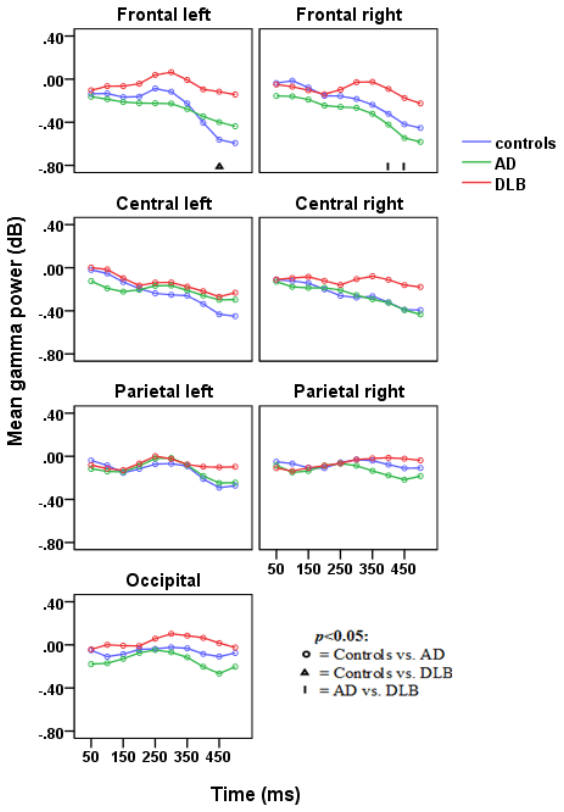


Figure 6.35. Mean gamma power (dB) for the post-incongruent target 500 ms interval across each region, for each group (controls, AD, DLB). The time points at which significant differences (p <0.05) between groups occurred are depicted on the plots (after correcting for multiple comparisons using Bonferroni correction).

The time x group interaction (Table 6.6), independent of region, is evident from Figure 6.36. The DLB group showed a lack of ERD relative to the controls between 350-500 ms, and the DLB ERD was less than that of the AD group in the initial 150 ms and between 300-500 ms. The ERSP of the controls and AD group was fairly comparable; the only difference was that the AD group showed greater ERD relative to controls in the initial 100 ms (Figure 6.36).

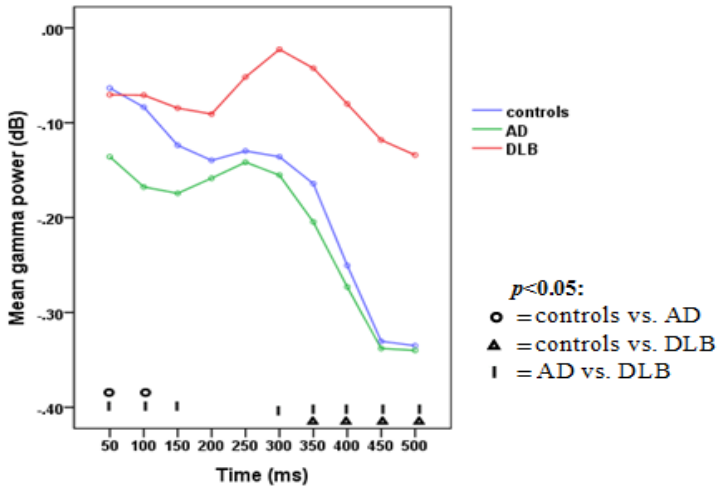


Figure 6.36. Mean gamma power (dB) for the post-incongruent target 500 ms interval, averaged across all regions, for each group. The time points at which significant differences (p <0.05) between groups occurred are depicted (after correcting for multiple comparisons using Bonferroni correction).

Incongruent target summary

- In the controls the ERSP associated with the incongruent target was broadly comparable to the congruent ERSP (across all frequency bands).
- There was less theta ERS in the DLB group relative to the controls in each region, across the vast majority of the 500 ms interval. In the majority of regions, the AD ERS was less than that of the controls at numerous successive time points (evident in a greater number of regions than in the congruent theta band).
- In the alpha band, there was an initial ERS followed by a later ERD. Although there was some inconsistency regarding the significant group differences when using the fixed alpha band and IAF, for both methods there was less ERS in the DLB group compared to both the controls and AD groups at 200 ms in the right parietal and occipital regions.
- There was less beta ERD in the DLB group relative to both the controls and AD group at numerous successive time points in the latter half of the 500 ms interval (particularly in the right hemisphere). There was less ERD in the AD group relative to the controls in the parietal regions (bilaterally).
- In the gamma range the controls showed a gradual ERD with increasing time. In the low gamma range, the control group ERD (averaged across all regions) was greater than that of the DLB and AD groups in the latter half of the 500ms interval. In the 55-90 Hz gamma range, the ERD across the 500ms was fairly comparable in the controls and AD groups; however there was a lack of ERD in the DLB group.

Chapter 7 . Oscillatory reactivity results: attentional networks

7.1 Behavioural results

The results of a brief behavioural analysis of the attentional network effects are shown in Table 7.1. There were no significant differences between the groups with regard to the magnitude of the alerting and orienting effects. Relative to the control group, the executive conflict effect was greater in the AD (p = 0.01) and DLB patients (p = 0.02), indicative of reduced executive conflict processing efficiency in the dementia patients. There was no difference between the dementia groups in terms of the magnitude of the executive conflict effect (p = 0.93). These findings demonstrate that from a behavioural perspective the attentional network effects in the EEG cohort were comparable to those reported in the larger cohort (chapter 3).

Table 7.1. Mean attentional network effects (ms) for each group. Standard deviations are presented in italics. The ANOVA results (Bonferroni corrected) show the significant between-group differences for each attentional network.

	Cohort			
Attentional network effect	**Controls (n=19)**	**AD (n=22)**	**DLB (n=24)**	**All group comparison**
Alerting	41.82 *(42.64)*	14.35 *(65.59)*	22.40 *(96.10)*	$F(2,62) = 0.78,\ p = 0.46$
Orienting	95.37 *(36.53)*	79.41 *(79.01)*	64.24 *(102.31)*	$F(2,62) = 0\ .79,\ p = 0.46$
Executive conflict	382.95 *(178.44)*	604.83 *(253.91)*	530.38 *(273.14)*	$F(2,62) = 4.49,\ p = 0.02$*

***** significant group differences (Bonferroni corrected pairwise comparisons)

7.2. Alerting effect ERSP

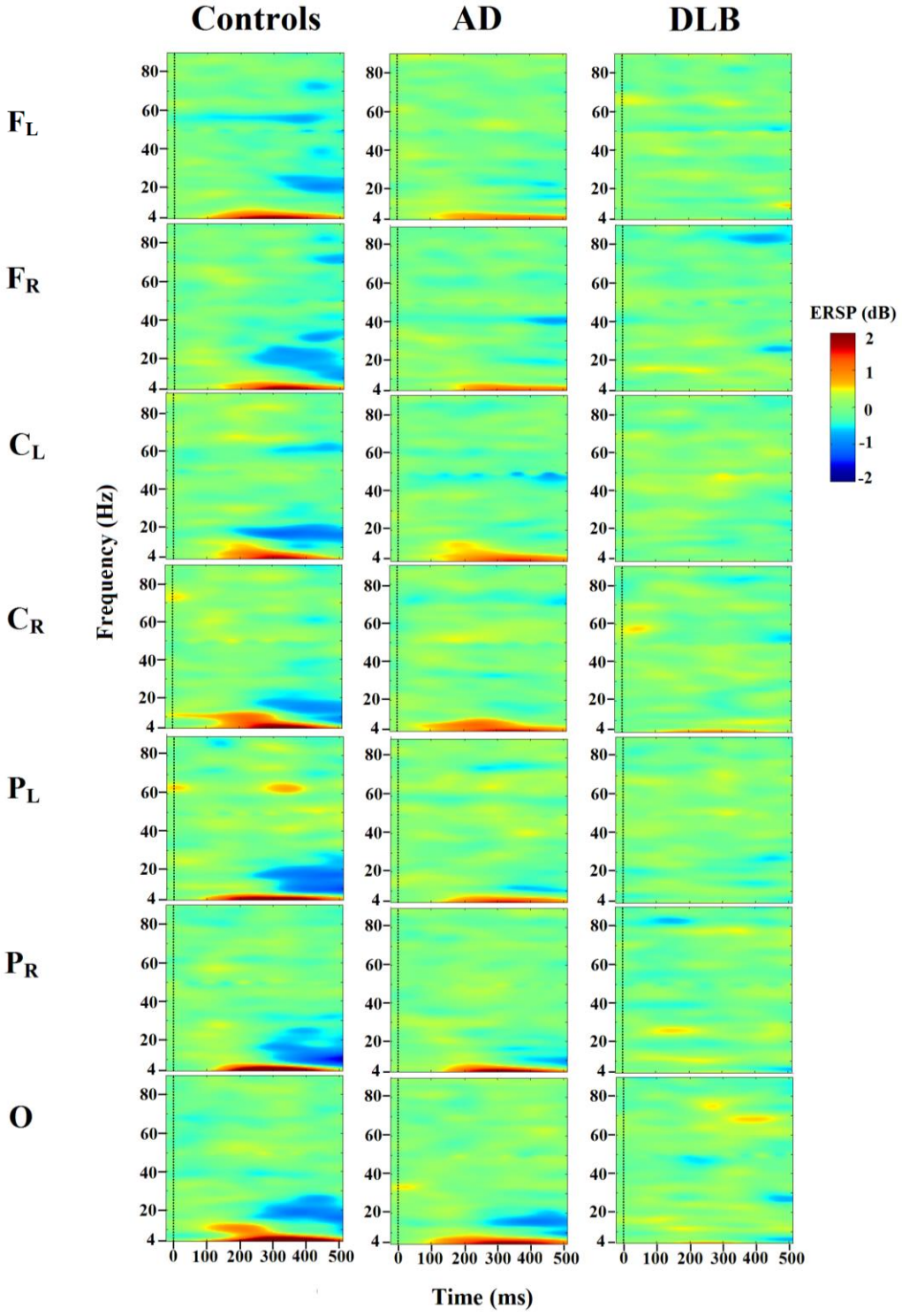


Figure 7.1. Heat maps showing time-frequency ERSP (event-related spectral perturbation) for the alerting effect, for each group (controls, AD, DLB), across each region. Power (dB) is plotted in colour (see scale); positive values represent event-related synchronisation, negative values represent event-related desynchronisation. The x axes represent time (ms) post-cue presentation, the vertical line at time 0 ms denotes the onset of the cue. The Y axes represent frequency (Hz) depicted from 4-90 Hz. F_L = Frontal left hemisphere, FR = Frontal right hemisphere, C_L= Central left hemisphere, C_R = Central right hemisphere, P_L = Parietal left hemisphere, P_R = Parietal right hemisphere, O = Occipital region.

Table 7.2. Results of the alerting effect ERSP repeated measures ANOVAs for each frequency band. The ANOVAs were conducted separately for each frequency band, with group (controls, AD, DLB) as the between-subjects factor, and time (10 intervals) and region (7 regions) as within-subject variables. Confidence intervals were adjusted using Bonferroni correction.

	Frequency band					
ANOVA factor	**Theta (4-7 Hz)**	**Alpha (8-14 Hz)**	**IAF (Individual alpha frequency)**	**Beta (14-30 Hz)**	**Low gamma (30-45 Hz)**	**Gamma (55-90 Hz)**
time	$F(2.1, 132.9) = 42.90$, $p < 0.001$**	$F(2.0,125.7) = 15.03$, $p < 0.001$**	$F(2.0,125.0) = 16.41$, $p < 0.001$**	$F(2.0, 121.1) = 32.31$, $p < 0.001$**	$F(3.4,210.2) = 4.29$, $p = 0.01$*	$F(3.2, 199.8) = 2.45$, $p = 0.06$
region	$F(6, 372) = 1.96$, $p = 0.07$	$F(6, 372) = 2.30$, $p = 0.03$*	$F(6, 372) = 4.11$, $p < 0.01$*	$F(6, 372) = 0.53$, $p < 0.01$*	$F(5.1, 316.6) = 0.96$, $p = 0.45$	$F(6, 372) = 2.04$, $p = 0.06$
time x region	$F(11.5, 714.7) = 2.97$, $p < 0.01$*	$F(14.0, 868.8) = 4.96$, $p < 0.001$**	$F(11.5,713.6) = 3.81$, $p < 0.001$**	$F(15.0,928.26) = 1.28$, $p = 0.21$	$F(15.4, 959.3) = 1.78$, $p = 0.03$*	$F(17.2,1064.4) = 2.90$, $p < 0.001$**
group	$F(2, 62) = 15.38$, $p < 0.001$**	$F(2, 62) = 0.14$, $p = 0.87$	$F(2, 62) = 1.29$, $p = 0.28$	$F(2, 62) = 4.23$, $p = 0.02$*	$F(2, 62) = 1.31$, $p = 0.28$	$F(2, 62) = 0.09$, $p = 0.91$
time x group	$F(4.3, 132.9) = 8.12$, $p < 0.001$**	$F(4.1,125.7) = 4.84$, $p < 0.01$*	$F(4.0, 125.0) = 2.88$, $p = 0.03$*	$F(3.9, 121.1) = 5.41$, $p < 0.01$*	$F(6.8,210.2) = 0.69$, $p = 0.68$	$F(6.4 199.8) = 1.51$, $p = 0.17$
region x group	$F(12, 372) = 0.76$, $p = 0.70$	$F(12, 372) = 2.07$, $p = 0.02$*	$F(12, 372) = 0.83$, $p = 0.62$	$F(12, 372) = 0.86$, $p = 0.66$	$F(5.1, 316.6) = 0.51$, $p = 0.89$	$F(12, 372) = 0.79$, $p = 0.77$
time x region x group	$F(23.1 714.7) = 1.70$, $p = 0.02$*	$F(28.0, 868.8) = 1.66$, $p = 0.05$	$F(23.0,713.6) = 1.43$, $p = 0.09$	$F(29.9,928.26) = 1.12$, $p = 0.30$	$F(30.9, 959.3) = 1.00$, $p = 0.47$	$F(34.3,1064.4) = 0.95$, $p = 0.56$

* = $p < 0.05$

= statistical trend ($p \leq 0.10$)

Alerting effect plot overview

Figure 7.1 depicts the mean ERSP associated with the alerting effect (the difference between the neutral cue and no cue ERSPs) for each group. In the controls there was a low frequency ERS (in the theta/alpha range), the onset time of this ERS varied with respect to region (the average onset being approximately 100 ms). In the central and occipital regions (in the controls) there was also a higher frequency ERS in the alpha/low beta range. This low frequency ERS was also observable across all regions in the AD group, however it was largely absent in the DLB group (with the exception of an ERS in the theta range visible in the right central region). In the controls there was an ERD in the alpha/beta range across all regions, evident from approximately 250 ms. In the AD group this ERD was apparent only in the posterior regions (and to a lesser extent relative to the controls), whilst in the DLB group the only ERD in this frequency range occurred in the occipital and right frontal regions between 400-500 ms. In the gamma range, the controls exhibited ERD primarily in the latter half of the 500 ms interval in the frontal regions bilaterally, and in the left central and left parietal regions (which was diffuse across the gamma frequency range). The controls also showed ERS activity in the gamma range, this was particularly apparent in the left parietal region between 60-70 Hz. In the AD group, there was clear ERD in the gamma range in the right frontal and left central regions between 40-45 Hz, and diffuse areas of ERS across all regions. In the DLB group ERD was most prominent in the right frontal region between 80-90 Hz at approximately 400-500 ms, and there was ERS in the occipital region at 70-80 Hz between 300-500 ms which was not apparent in the controls or AD group. As discussed in chapter 5 (section 5.4), for each of the attentional networks only significant results (and statistical trends) are discussed in detail, and thus the alerting effect significant results from Table 7.2 are discussed below.

Alerting effect theta ERSP

In the theta band there was a main effect of time (Table 7.2), from Figure 7.2 it can be seen that this was due to the ERS which was evident across all regions and peaked at approximately 300 ms. The occipital ERS peaked slightly later than the other regions (at approximately 350 ms), thus explaining the significant time x region interaction. The trend for

a region effect (Table 7.2.) is explicable in terms of the greater ERS power in the posterior regions relative to the frontal regions (Figure 7.2).

The main effect of group (Table 7.2.) was due to a lack of ERS (across all regions) in the DLB group relative to both the controls (p <0.001) and AD group (p <0.001), there was no difference between the ERS of the AD and control groups (p = 0.65). The group interactions (time x group, time x region x group) are apparent when observing the significant group differences depicted in Figure 7.2. In each region, there were numerous consecutive time points at which the DLB ERS was less than that of the controls (although there was no region in which the ERS of these two groups was significantly different in the initial 100 ms). As shown in Figure 7.2, there were no significant differences between the controls and AD group (in any region). For the majority of the time points at which the DLB ERS was less than the controls, this lack of DLB ERS was also significantly less than the that of the AD group (particularly in the more posterior regions). Therefore, a lack of theta ERS associated with the alerting effect is characteristic of the DLB group.

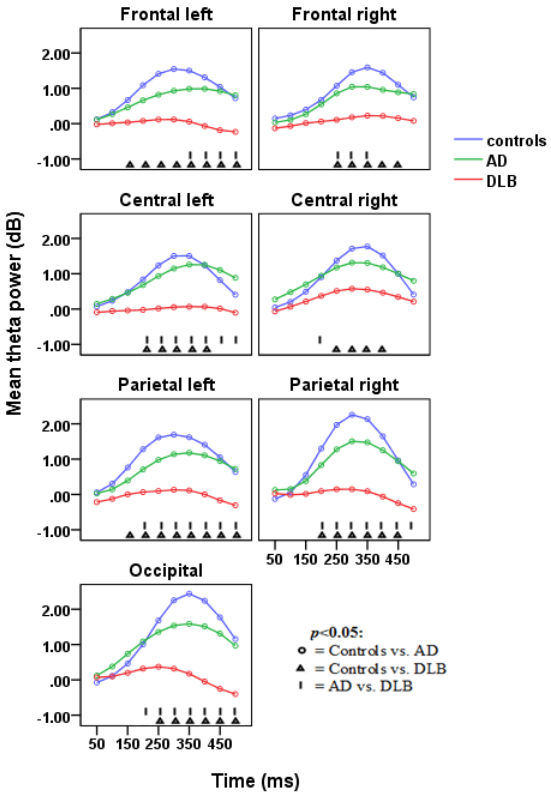


Figure 7.2. Mean theta power (dB) associated with the alerting effect for the post cue 500 ms interval across each region, for each group (controls, AD, DLB). The time points at which significant differences (p <0.05) between groups occurred are depicted on the plots (after correcting for multiple comparisons using Bonferroni correction).

Alerting effect alpha ERSP

The power plots for the fixed alpha band are shown in Figure 7.3, whilst the IAF power plots are depicted in Figure 7.4.

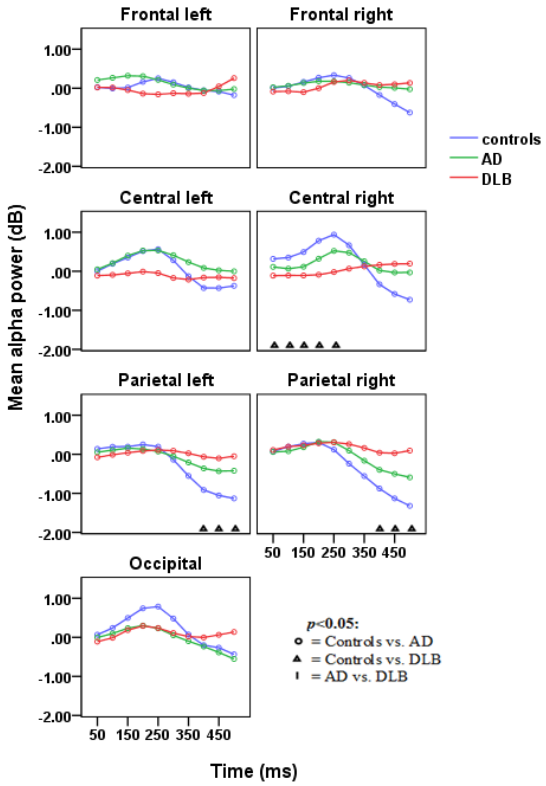


Figure 7.3. Mean alpha power (dB) associated with the alerting effect for the post cue 500 ms interval across each region, for each group (controls, AD, DLB). The time points at which significant differences (p <0.05) between groups occurred are depicted on the plots (after correcting for multiple comparisons using Bonferroni correction).

Table 7.2 shows that for both the fixed alpha band and IAF there was a main effect of region, from Figures 7.3 and 7.4 it is evident that there was less alpha ERSP in the frontal regions relative to the other regions. The main effect of time (Table 7.2) was due to an initial ERS in the first half of the 500 ms interval, followed by an ERD in the latter half. The early ERS was only present in some of the regions (the occipital and left and right central regions), and the ERD was greatest in the parietal regions (bilaterally), hence the significant time x region interaction.

For both the fixed alpha band and IAF there was a significant time x group interaction, however the region interactions (region x group, time x region x group) were only significant when using the fixed alpha band, although there was a trend for a time x region x group

interaction when using IAF (Table 7.2). The only significant differences between groups when using the fixed alpha band were differences in ERSP between the DLB group and the controls (Figure 7.3). There was less ERD in the DLB group relative to the controls between 400-500 ms in the parietal regions (bilaterally), and less ERS in the DLB group compared to the controls in the initial 250 ms in the right central region. Figure 7.4 shows that for the IAF group differences were evident in the right central and bilateral parietal regions (the same regions as the fixed alpha band). In the right central region the DLB group had less early ERS relative to the controls (comparable to the fixed alpha band), however this lack of ERS was also less than the AD group when using IAF. In the right parietal region, there was less late ERD in the DLB group relative to the controls, however there were less time points at which this difference was significant when using the IAF relative to the fixed alpha band. An obvious difference between the fixed alpha and IAF group differences is in the left parietal region; when using the IAF the later ERD difference between the controls and DLB was no longer significant, however Figure 7.4 shows that there was greater ERD in the DLBs relative to the controls in the initial 50 ms.

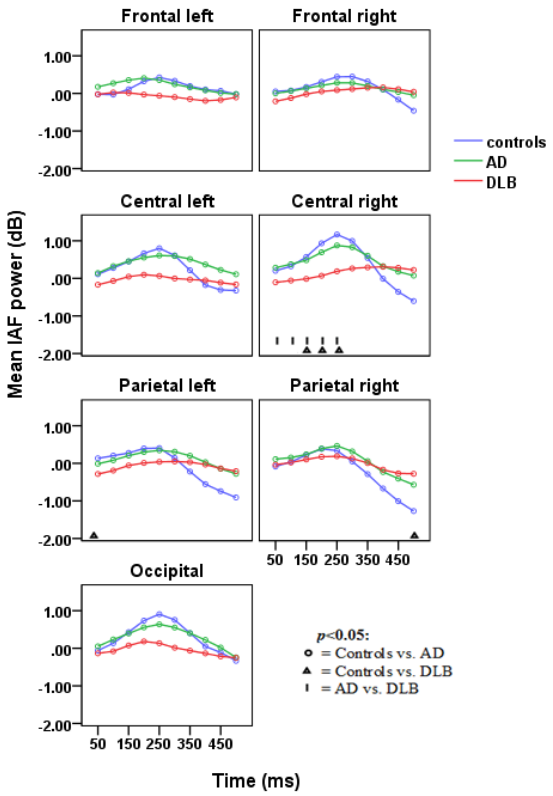


Figure 7.4. Mean IAF power (dB) associated with the alerting effect for the post cue 500 ms interval across each region, for each group (controls, AD, DLB). The time points at which significant differences (p <0.05) between groups occurred are depicted on the plots (after correcting for multiple comparisons using Bonferroni correction).

Alerting effect beta ERSP

Table 7.2 shows that for the beta ERSP there was a significant effect of time; from Figure 7.5 it is clear that this was due an ERD evident from approximately 200-250 ms across all regions. There was also an early ERS, although of a much smaller power relative to the later ERD. Variability in the ERSP activity with respect to region explains the significant region effect; the ERD power in the right central region appears to be less than that of the other regions.

There were significant group, and time x group effects (Table 7.2), however the group interactions with region were not significant, indicating that the group interactions with time were relatively comparable across regions. The overall group effect was due to a lack of ERD in the DLB group relative to the controls ($p = 0.02$), whilst there was no difference between the AD and DLB group ($p = 1.00$), or controls and AD group ERD ($p = 0.15$). From the significant group differences (shown in Figure 7.5), it is apparent that the group interactions with time were primarily due to less ERD in the DLB group relative to the controls in the latter half of the 500 ms interval (which was significant in all regions except the left parietal region). In the occipital region, the DLB group ERD was also significantly less than that of the AD group between 300-500 ms, thus this aberrant beta activity differentiates the DLBs from both the controls and AD group. The only difference between the controls and AD beta activity was in the left hemisphere; the AD ERD was less than that of the controls in the left central region between 300-350 ms, and at 300 ms in the left parietal region. Given that the region x group interactions were not significant, these group differences in each region must be treated with caution.

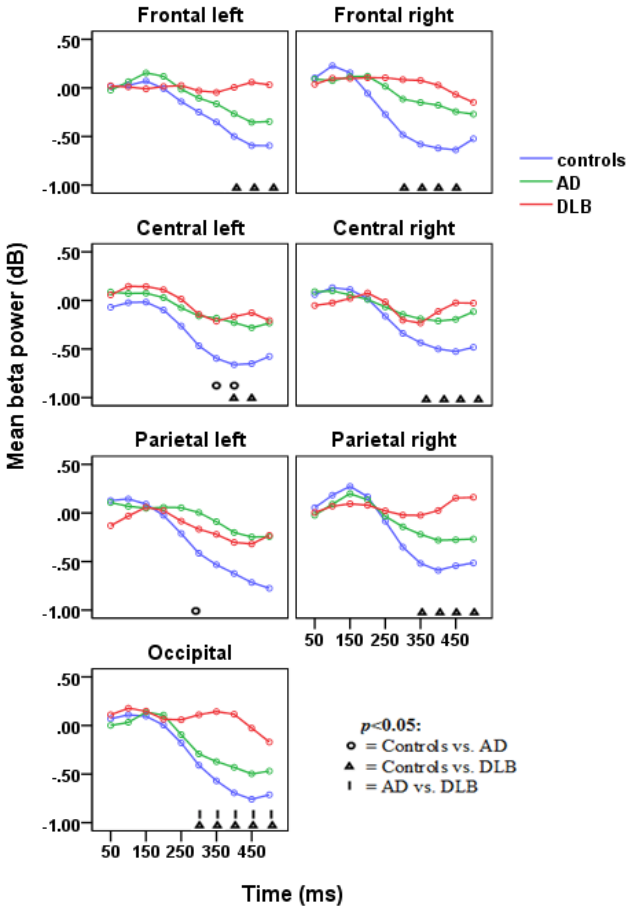


Figure 7.5. Mean beta power (dB) associated with the alerting effect for the post cue 500 ms interval across each region, for each group (controls, AD, DLB). The time points at which significant differences (p <0.05) between groups occurred are depicted on the plots (after correcting for multiple comparisons using Bonferroni correction).

Alerting effect gamma ERSP

The low gamma (30-45 Hz) power plots for each group are depicted in Figure 7.6, and the power plots for the 55-90 Hz gamma interval are shown in Figure 7.7.

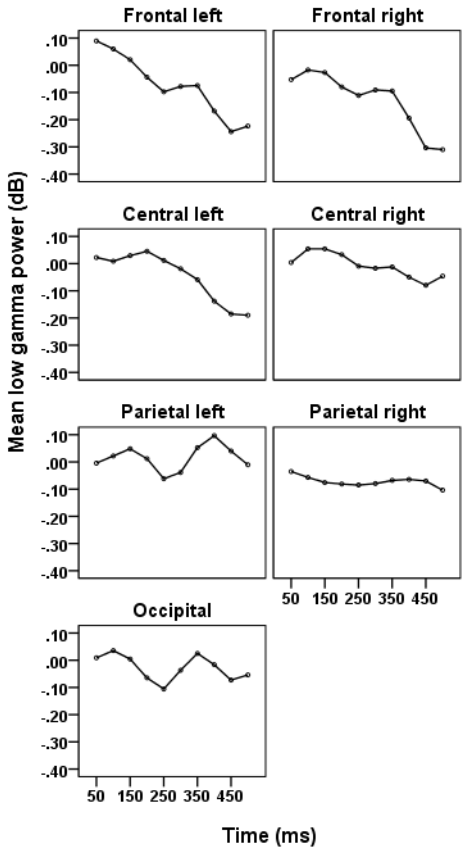


Figure 7.6. Mean low gamma power (dB) associated with the alerting effect for the post cue 500 ms interval in each region, averaged across all groups.

In the low gamma band there was a significant effect of time (across all groups) (Table 7.2), although there was a greater degree of variability across the time range relative to the lower frequencies; over the whole 500 ms interval there was a trend for a gradual ERD with increasing time. When averaged across all groups (Figure 7.6) it is evident that this ERD was most apparent in the anterior regions (especially the frontal and left central regions), hence the significant time x region interaction.

In the 55-90 Hz gamma range, whilst there were trends for time and region effects, the time x region interaction was highly significant (Table 7.2); across all groups there was a gradual ERD evident in the frontal regions, whilst in the right central, left parietal and occipital regions there appeared to be ERS activity (at varying time intervals between these regions) (Figures 7.7).

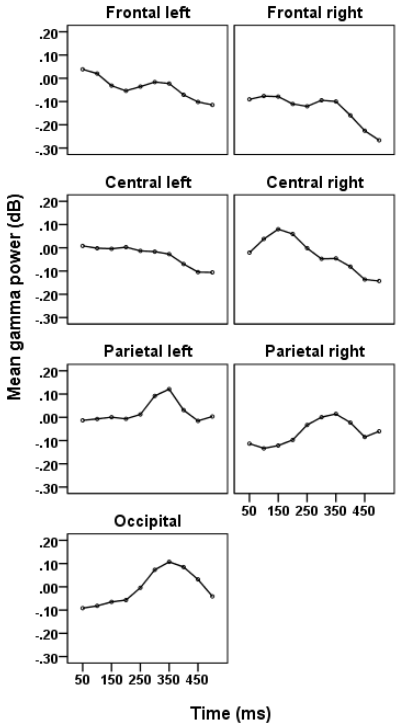


Figure 7.7. Mean gamma power (dB) associated with the alerting effect for the post cue 500 ms interval for each region, averaged across all groups.

7.2.1 Alerting effect clinical correlations

The ERSP values used in the alerting effect theta and beta correlation analyses (see below) were derived from the time points at which there were significant group differences (depicted in Figures 7.2 and 7.5 respectively).

Theta

For the DLB group, the mean theta ERSP positively correlated with the CAMCOG and MMSE total score as follows: between 350-500 ms in the left frontal region (CAMCOG: $r = 0.52$, $p = 0.02$, MMSE: $r = 0.43$, $p = 0.05$), between 250-350 ms in the right frontal region (CAMCOG: $r = 0.54$, $p = 0.01$, MMSE: $r = 0.54$, $p = 0.01$), between 250-450 ms in the right parietal region (CAMCOG: $r = 0.45$, $p = 0.03$, MMSE: $r = 0.44$, $p = 0.04$), and between 250-500 ms in the occipital region (CAMCOG: $r = 0.58$, $p < 0.01$, MMSE: $r = 0.54$, $p < 0.01$). These results indicate that in the DLB group the lack of ERS in the bilateral frontal, right parietal and occipital regions (in the specified time intervals which differentiated the DLB theta from the AD and control groups) was associated with lower MMSE and CAMCOG scores. In the DLB group, there was also a negative correlation between the ERSP in the right parietal region between 200-450 ms and the total CAF score ($r = -0.46$, $p = 0.03$).

Beta

In the DLB group there were positive correlations between the mean ERSP and the total UPDRS score; between 300-450 ms in the right frontal region ($r = 0.51$, $p = 0.02$), and between 400-450 ms in the left central region ($r = 0.45$, $p = 0.03$).

Alerting effect ERSP summary

- In the theta range there was a broad ERS evident across the 500 ms interval in all regions. In each region, there were numerous consecutive time points (particularly the latter half of the 500 ms interval) at which the lack of ERS in the DLB group was significantly less than both the controls and AD groups. Therefore, a lack of theta ERS (across all regions) is characteristic of the DLB group. This lack of ERS in the DLB group was associated with lower CAMCOG and MMSE scores at varying time points in the bilateral frontal, right parietal and occipital regions. In the right parietal region between 200-450 ms the reduced ERS in the DLB group was associated with greater severity of cognitive fluctuations (as measured by the total CAF score).
- In the alpha range there was a lack of ERD in the DLB group relative to the controls bilaterally in the parietal regions (the significant time points differed according to whether the fixed alpha band or IAF was used). In the right central region, there was a lack of initial ERS in the DLB group which was evident irrespective of the alpha band method used.
- In the beta range there was an ERD in the latter half of 500 ms across all regions. In the occipital region, the lack of DLB ERD in the latter half of the 500 ms differentiates the DLB beta activity from that of the controls and AD group. The lack of DLB ERD in the latter time points in the right frontal and left central regions was associated with a high UPDRS total score.
- In the gamma range, there was much greater ERSP variability across the 500 ms interval (in each region) relative to the lower frequencies, as well as less overall ERSP power.
- For the alerting effect the only ERSP difference between the controls and AD group was less beta ERD in the AD group in the left central and left parietal regions. Therefore, atypical ERSP associated with the alerting effect is primarily characteristic of DLB.

7.3 Orienting effect ERSP

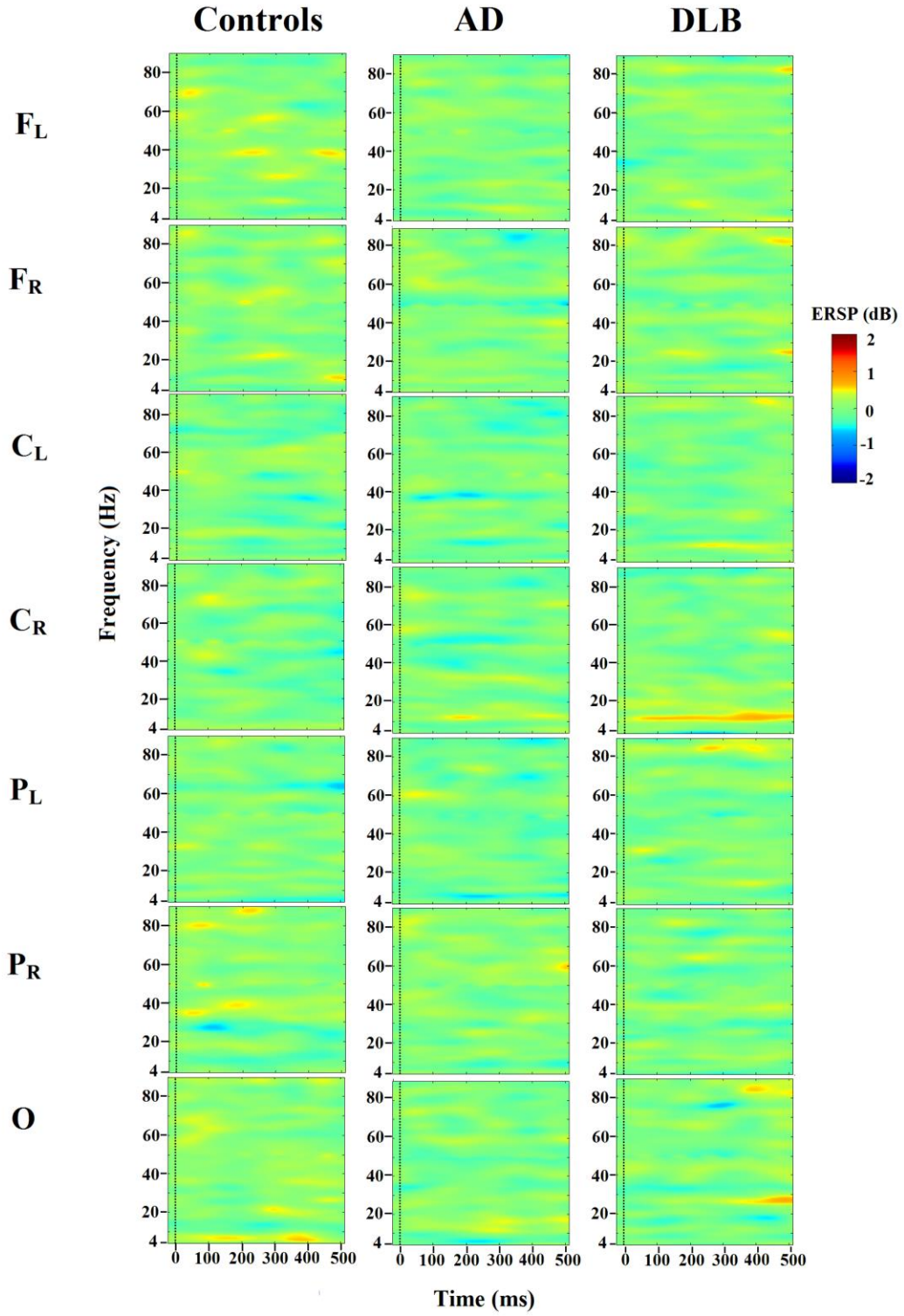


Figure 7.8. Heat maps showing time-frequency ERSP (event-related spectral perturbation) for the orienting effect, for each group (controls, AD, DLB), across each region. Power (dB) is plotted in colour (see scale); positive values represent event-related synchronisation, negative values represent event-related desynchronisation. The x axes represent time (ms) post-cue presentation, the vertical line at time 0 ms denotes the onset of the cue. The Y axes represent frequency (Hz) depicted from 4-90 Hz. F_L = Frontal left hemisphere, FR = Frontal right hemisphere, C_L= Central left hemisphere, C_R = Central right hemisphere, P_L = Parietal left hemisphere, P_R = Parietal right hemisphere, O = Occipital region.

Table 7.3. Results of the orienting effect ERSP repeated measures ANOVAs for each frequency band. The ANOVAs were conducted separately for each frequency band, with group (controls, AD, DLB) as the between-subjects factor, and time (10 intervals) and region (7 regions) as within-subject variables. Confidence intervals were adjusted using Bonferroni correction.

	Frequency band					
ANOVA factor	**Theta (4-7 Hz)**	**Alpha (8-14 Hz)**	**IAF (Individual alpha frequency)**	**Beta (14-30 Hz)**	**Low gamma (30-45 Hz)**	**Gamma (55-90 Hz)**
time	$F(2.6, 162.7) = 4.13$ $p = 0.01$*	$F(2.9, 180.3) = 0.57$, $p = 0.63$	$F(2.8, 173.8) = 1.35$, $p = 0.26$	$F(3.1, 193.1) = 0.52$, $p = 0.68$	$F(3.6, 220.5) = 0.91$, $p = 0.45$	$F(4.2, 258.6) = 4.39$, $p < 0.01$*
region	$F(5.1, 313.2) = 1.09$ $p = 0.37$	$F(6, 372) = 1.77$, $p = 0.11$	$F(6, 372) = 1.16$, $p = 0.33$	$F(5.01, 310.7) = 1.19$, $p = 0.32$	$F(6, 372) = 1.45$, $p = 0.20$	$F(6, 372) = 2.07$, $p = 0.06$
time x region	$F(12.6,781.8) = 0.49$, $p = 0.93$	$F(14.2,882.1) = 0.96$, $p = 0.49$	$F(12.9, 801.9) = 0.96$, $p = 0.49$	$F(16.9, 1050.2) = 1.06$, $p = 0.39$	$F(15.8, 980.2) = 1.49$, $p = 0.10$	$F(15.9, 982.6) = 0.60$, $p = 0.89$
group	$F(2, 62) = 0.37$, $p = 0.37$	$F(2, 62) = 1.30$, $p = 0.28$	$F(2, 62) = 1.18$, $p = 0.31$	$F(2, 62) = 0.11$, $p = 0.90$	$F(2, 62) = 0.49$, $p = 0.61$	$F(2, 62) = 0.84$, $p = 0.44$
time x group	$F(5.2, 162.7) = 0.44$ $p = 0.83$	$F(5.8, 180.3) = 0.65$ $p = 0.68$	$F(5.6, 173.8) = 0.60$, $p = 0.72$	$F(6.2, 193.1) = 0.31$, $p = 0.94$	$F(7.1, 220.5) = 0.38$, $p = 0.92$	$F(8.3, 258.6) = 1.54$, $p = 0.14$
region x group	$F(10.1, 313.2) = 1.52$, $p = 0.13$	$F(12, 372) = 1.34$, $p = 0.21$	$F(12, 372) = 0.80$, $p = 0.66$	$F(10.0, 310.7) = 1.00$, $p = 0.44$	$F(12, 372) = 0.71$, $p = 0.74$	$F(12, 372) = 0.90$, $p = 0.54$
time x region x group	$F(25.2 781.8) = 0.59$, $p = 0.95$	$F(28.5,882.1) = 1.34$, $p = 0.11$	$F(25.9, 801.9) = 1.21$, $p = 0.22$	$F(33.9, 1050.2) = 1.32$, $p = 0.12$	$F(31.6, 980.2) = 0.82$, $p = 0.76$	$F(31.7, 982.6) = 0.96$, $p = 0.54$

* = $p < 0.05$

= statistical trend ($p \leq 0.10$)

Orienting effect plot overview

From Figure 7.8 it is apparent that the ERSP associated with the orienting effect was more diffuse across the time and frequency domains relative to the alerting effect. In the controls, there was low frequency (theta) ERS in the occipital region between approximately 100-200 ms and 300-400 ms. There was also higher frequency ERS, extending into the gamma range, predominantly in the right parietal and frontal regions. The controls also exhibited an ERD in the right parietal region around 30 Hz at approximately 100 ms, as well as left parietal ERD in the gamma range at 500 ms. The ERSP in the dementia groups was broadly comparable to the controls in the sense that the oscillatory reactivity primarily comprised diffuse ERS (across all regions). The power of this orienting effect ERSP was fairly comparable across the groups, and was less than that of the ERSP associated with the alerting effect. Notable differences between the groups included occipital ERS in the DLB group in the beta and gamma range from approximately 300 ms, as well as a gamma ERD between 250-300 ms which was not apparent in the control and AD groups. Of particular interest is the alpha/low beta ERS evident in the DLB group in the right central region, visible across the whole 500 ms interval. The results of the frequency band analyses (Table 7.3) show that these apparent group differences were not, however, statistically significant. However, there were significant time effects in the theta and gamma bands.

Orienting effect theta ERSP

In the theta band, the significant effect of time was due to a broad ERD across the 500 ms interval (evident in all of the groups) which peaked between approximately 200-300 ms (Figure 7.9). There were no significant group effects.

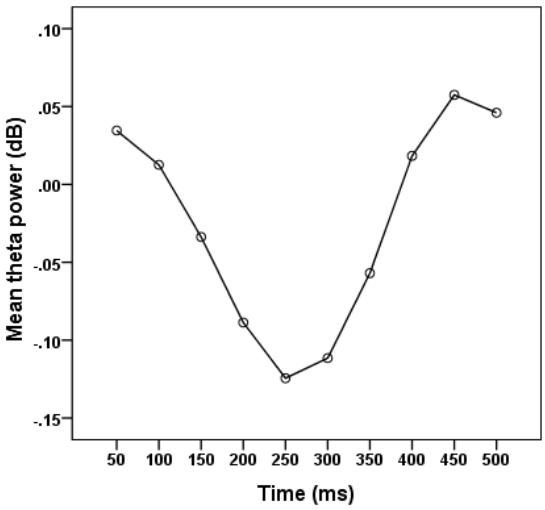


Figure 7.9. Mean theta power (dB) associated with the orienting effect for the post cue 500 ms interval, averaged across all regions and all groups.

Orienting effect gamma ERSP

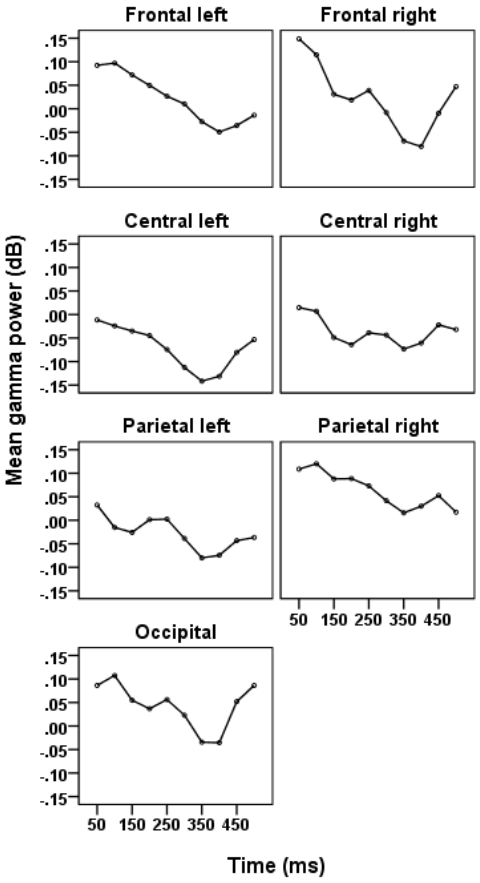


Figure 7.10. Mean gamma power (dB) associated with the orienting effect for the post cue 500 ms for each region, averaged across all groups.

In the 55-90 Hz gamma range there was a significant effect of time, and a trend for a main effect of region (Table 7.3). From Figure 7.10 it can be seen that the time effect is explicable in terms of a gradual ERD with increasing time; however there was substantial ERSP variability across regions, thus explaining the trend for a region effect.

Orienting effect summary

- For the orienting effect (the difference between the neutral cue and spatial cue ERSP) there were no overall significant differences between the groups for any of the frequency bands. Therefore, although there were group differences evident for the neutral and spatial cues (the absolute ERSP associated with the cues), the relative ERSP difference between the cues was not significant.
- There were significant time effects in the theta and gamma bands. In the theta range the orienting effect was associated with an ERD which peaked at approximately 250 ms post-stimulus onset (across all groups). In the gamma band there was a gradual ERD with increasing time which peaked between 350-400 ms.

7.4 Executive conflict effect ERSP

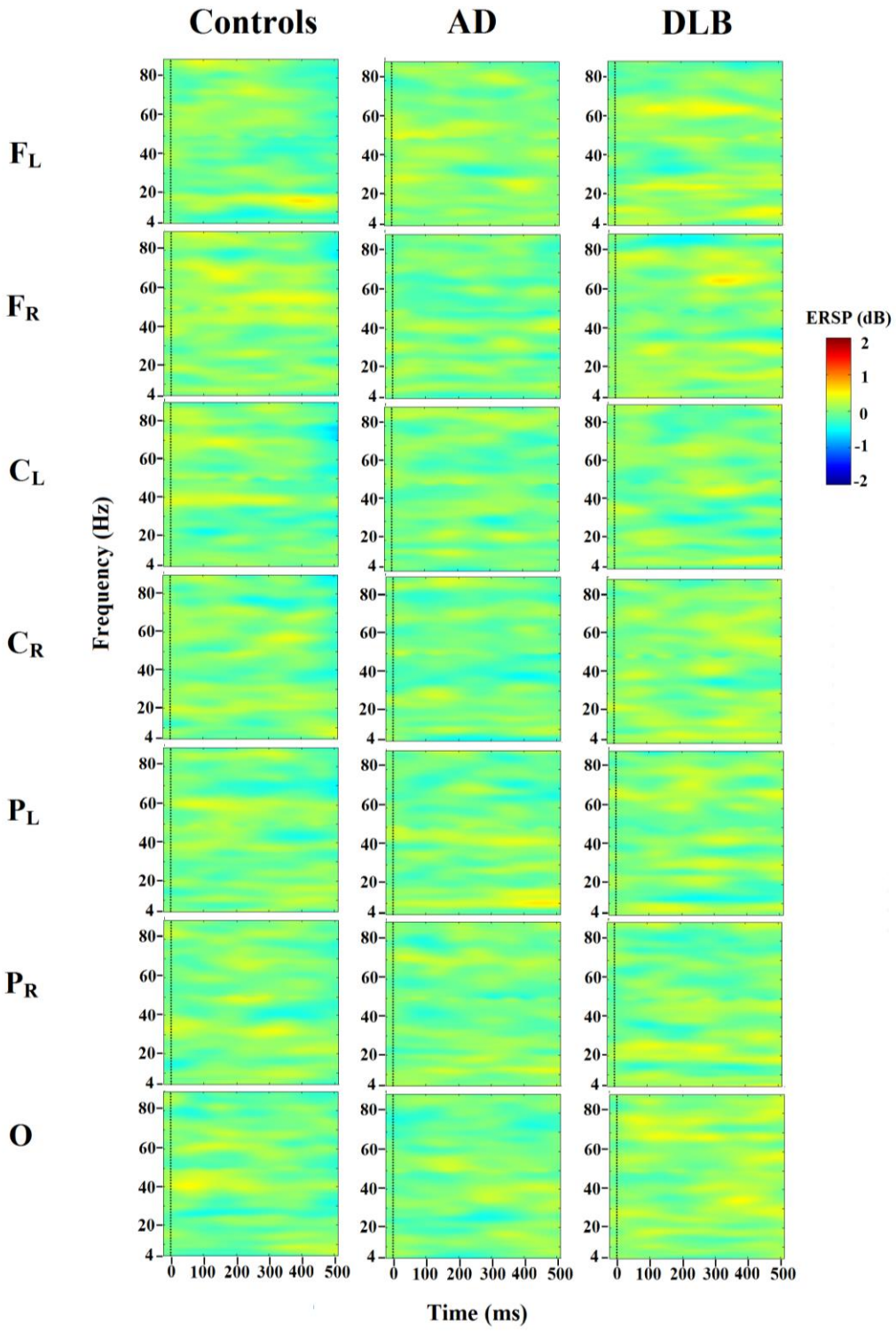


Figure 7.11. Heat maps showing time-frequency ERSP (event-related spectral perturbation) for the executive conflict effect, for each group (controls, AD, DLB), across each region. Power (dB) is plotted in colour (see scale); positive values represent event-related synchronisation, negative values represent event-related desynchronisation. The x axes represent time (ms) post-target presentation, the vertical line at time 0 ms denotes the onset of the target. The Y axes represent frequency (Hz) depicted from 4-90 Hz. F_L = Frontal left hemisphere, FR = Frontal right hemisphere, C_L= Central left hemisphere, C_R = Central right hemisphere, P_L = Parietal left hemisphere, P_R = Parietal right hemisphere, O = Occipital region.

Table 7.4. Results of the executive conflict ERSP repeated measures ANOVAs for each frequency band. The ANOVAs were conducted separately for each frequency band, with group (controls, AD, DLB) as the between-subjects factor, and time (10 intervals) and region (7 regions) as within-subject variables. Confidence intervals were adjusted using Bonferroni correction.

	Frequency band					
ANOVA factor	**Theta (4-7 Hz)**	**Alpha (8-14 Hz)**	**IAF (Individual alpha frequency)**	**Beta (14-30 Hz)**	**Low gamma (30-45 Hz)**	**Gamma (55-90 Hz)**
time	$F(2.5, 155.9) = 1.12$, $p = 0.34$	$F(3.2,197.2) = 3.66$, $p = 0.10$	$F(2.7, 169.5) = 1.24$, $p = 0.30$	$F(3.1,190.0) = 0.43$, $p = 0.73$	$F(3.6, 224.2) = 0.88$, $p = 0.47$	$F(3.1, 194.8) = 2.36$, $p = 0.07$
region	$F(6, 372) = 1.24$, $p = 0.29$	$F(6, 372) = 0.15$, $p = 0.99$	$F(6, 372) = 1.07$, $p = 0.38$	$F(4.9,303.3) = 2.50$, $p = 0.03$*	$F(6, 372) = 2.30$, $p = 0.04$*	$F(6, 372) = 0.45$, $p = 0.85$
time x region	$F(11.9, 739.4) = 1.80$, $p = 0.05$	$F(15.2,944.3) = 0.94$, $p = 0.52$	$F(13.3,823.0) = 1.03$, $p = 0.42$	$F(15.2,940.8) = 1.26$, $p = 0.22$	$F(15.9, 982.8) = 1.26$, $p = 0.22$	$F(17.1, 1057.2) = 0.02$, $p = 0.03$*
group	$F(2, 62) = 1.59$, $p = 0.21$	$F(2, 62) = 0.45$, $p = 0.64$	$F(2, 62) = 1.07$, $p = 0.35$	$F(2, 62) = 1.27$, $p = 0.29$	$F(2, 62) = 0.01$, $p = 0.99$	$F(2, 62) = 1.47$, $p = 0.24$
time x group	$F(5.0, 155.9) = 1.06$, $p = 0.39$	$F(6.4,197.2) = 0.72$, $p = 0.64$	$F(5.5, 169.5) = 1.03$, $p = 0.41$	$F(6.1,190.0) = 0.78$, $p = 0.59$	$F(7.2, 224.2) = 2.06$, $p = 0.05$	$F(6.3, 194.8) = 2.30$, $p = 0.03$*
region x group	$F(12, 372) = 1.14$, $p = 0.33$	$F(12, 372) = 1.30$, $p = 0.22$	$F(12, 372) = 0.58$, $p = 0.86$	$F(9.8,303.3) = 0.74$, $p = 0.68$	$F(12, 372) = 0.79$, $p = 0.64$	$F(12, 372) = 1.33$, $p = 0.20$
time x region x group	$F(23.9, 739.4) = 1.23$ $p = 0.21$	$F(30.5,944.3) = 1.11$, $p = 0.31$	$F(26.6,823.0) = 1.02$, $p = 0.44$	$F(30.3,940.8) = 0.86$, $p = 0.69$	$F(31.7, 982.8) = 1.27$, $p = 0.15$	$F(34.1, 1057.2) = 0.81$, $p = 0.78$

* = $p < 0.05$

= statistical trend ($p \leq 0.10$)

Executive conflict effect plot overview

The time-frequency decomposition plots shown in Figure 7.11 depict the ERSP associated with the executive conflict effect (the difference between the congruent and incongruent target ERSP). In the controls it is apparent that the executive conflict effect oscillatory activity mainly comprised ERS, which was widely dispersed across the time and frequency domains, and visible in all regions. This was also the case for the AD and DLB groups, from the plots it appears that the mean reactivity was broadly comparable across all three groups. Table 7.4 shows that the only significant group differences were in the gamma frequency range. All of the significant effects and statistical trends listed in Table 7.4 are discussed in the following sections.

Executive conflict effect theta ERSP

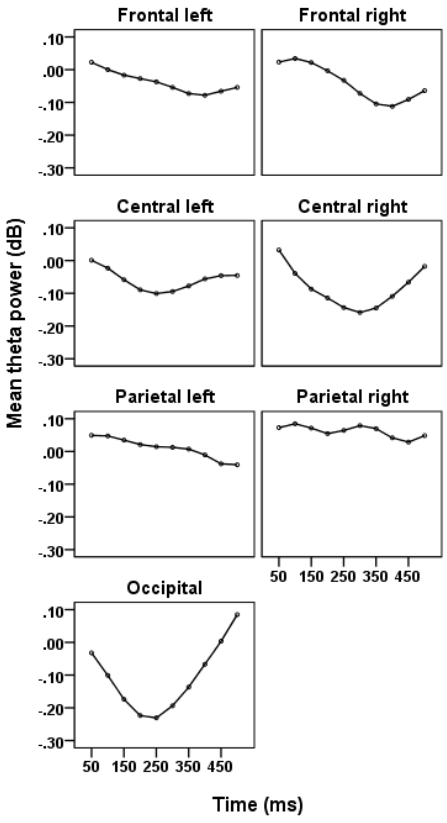


Figure 7.12. Mean theta power (dB) associated with the executive conflict effect for the post-target 500 ms interval across each region, averaged across all groups.

From Figure 7.12 (the average ERSP across all groups) it is apparent that in the theta range there was substantial ERSP variability with respect to time across the regions, this explains the significant time x region interaction (Table 7.4). There was notable ERD in the occipital and right central regions which peaked between approximately 200-300 ms.

Executive conflict effect alpha ERSP

For the fixed alpha band there were no group effects, however there was a trend for a main effect of time (across all regions and groups); Figure 7.13 shows that this was due to an initial ERS which peaked at approximately 150 ms, followed by an ERD which peaked at approximately 300 ms, and then a gradual ERS up to 500 ms.

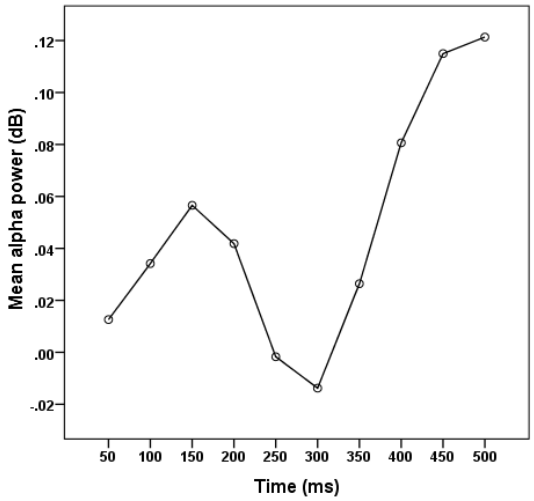


Figure 7.13. Mean alpha power (dB) associated with the executive conflict effect for the post-target 500 ms interval, averaged across all groups and all regions.

Executive conflict beta ERSP

In the beta range there was a main effect of region. This region effect may be partially driven by the apparent lack of reactivity in the frontal regions (Figure 7.14), however exploratory statistical analyses (not reported) indicated that this was not significant.

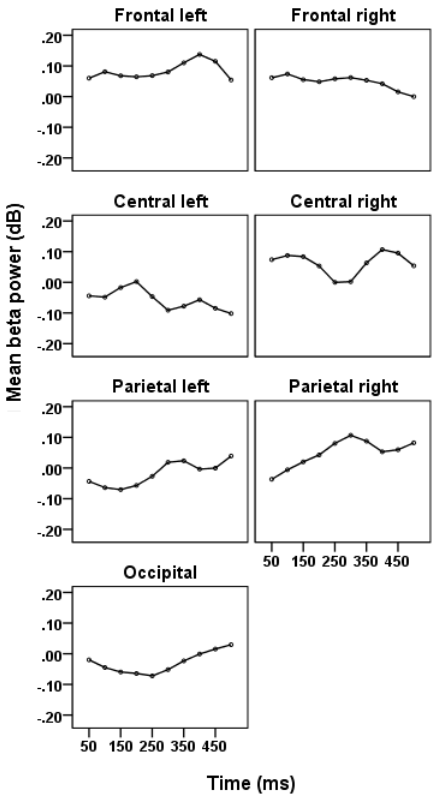


Figure 7.14. Mean beta power (dB) associated with the executive conflict effect for the post-target 500 ms interval across each region, averaged across all groups.

Executive conflict effect gamma ERSP

In the low gamma range, although there was a region effect (Table 7.4), from Figure 7.15 (the ERSP averaged across all groups) it is apparent that there was substantial variability in the ERSP across the regions, and exploratory statistical analyses comparing the ERSP of each region indicated that there were no significant differences between the regions.

There was a trend for a time x group interaction (Table 7.4); Figure 7.16 shows that when considering the average ERSP across all regions there was significantly less ERS in the AD group relative to controls at 50 ms, and less ERD in the AD group relative to the controls at 500 ms.

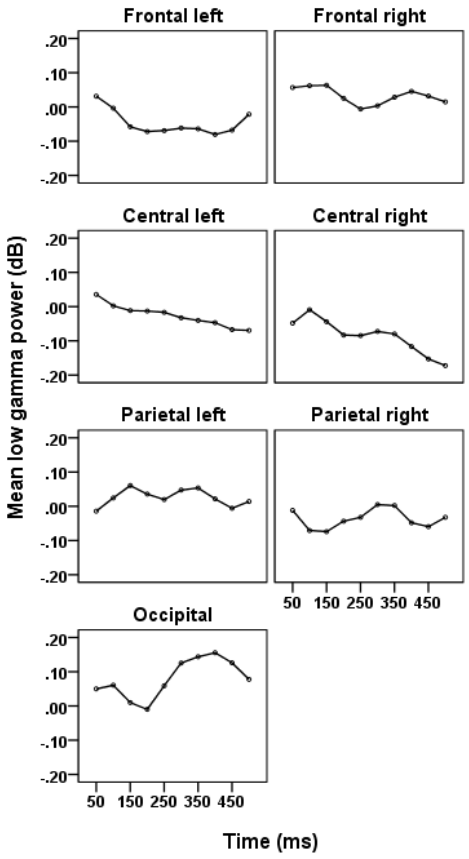


Figure 7.15. Mean low gamma power (dB) associated with the executive conflict effect for the post-target 500 ms interval across each region, averaged across all groups.

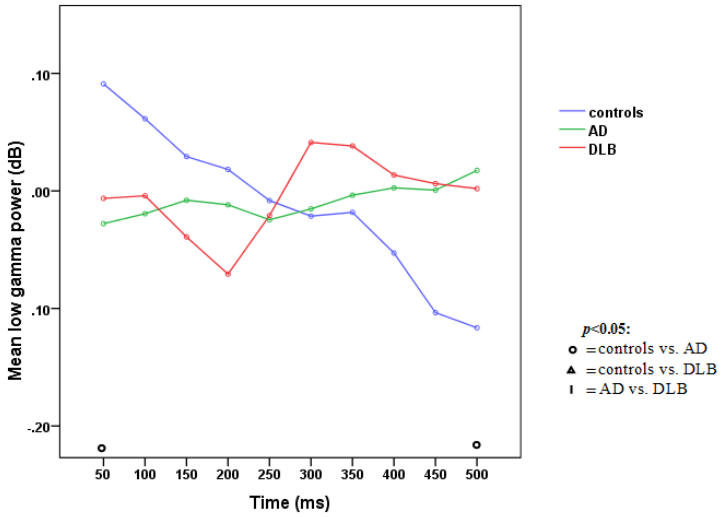


Figure 7.16. Mean low gamma power (dB) associated with the executive conflict effect for the post-target 500 ms interval for each group, averaged across all regions. The time points at which significant differences (p <0.05) between groups occurred are depicted on the plots (after correcting for multiple comparisons using Bonferroni correction).

In the 55-90 Hz gamma band there was a significant time x region interaction (Table 7.4); from Figure 7.17 is evident that there was substantial ERSP variability in the 500 ms interval with respect to region.

The significant time x group effect (Table 7.4) is evident from the group differences (independent of region) depicted in Figure 7.18. There was a lack of DLB ERD relative to the controls and AD group between 400-500 ms, and relative to the AD group in the initial 100 ms. The AD group showed greater ERD relative to the controls in the initial 150 ms.

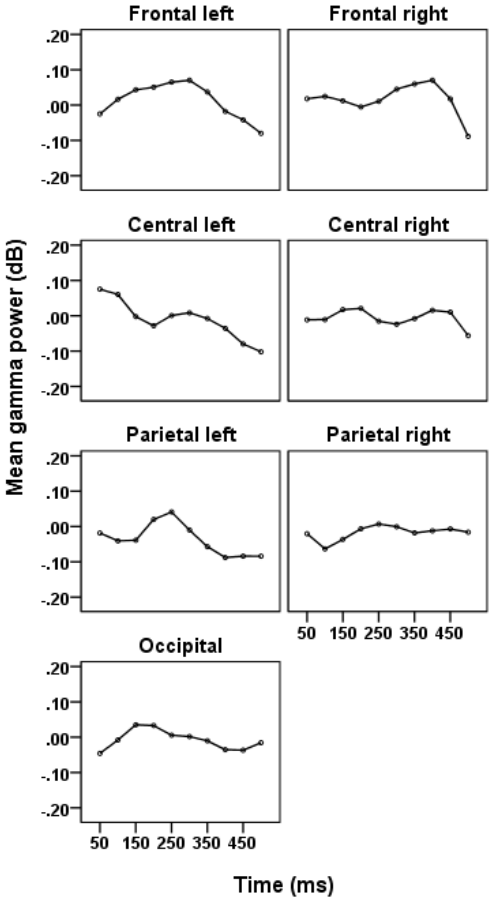


Figure 7.17. Mean gamma power (dB) associated with the executive conflict effect for the post-target 500 ms interval across each region, averaged across all groups.

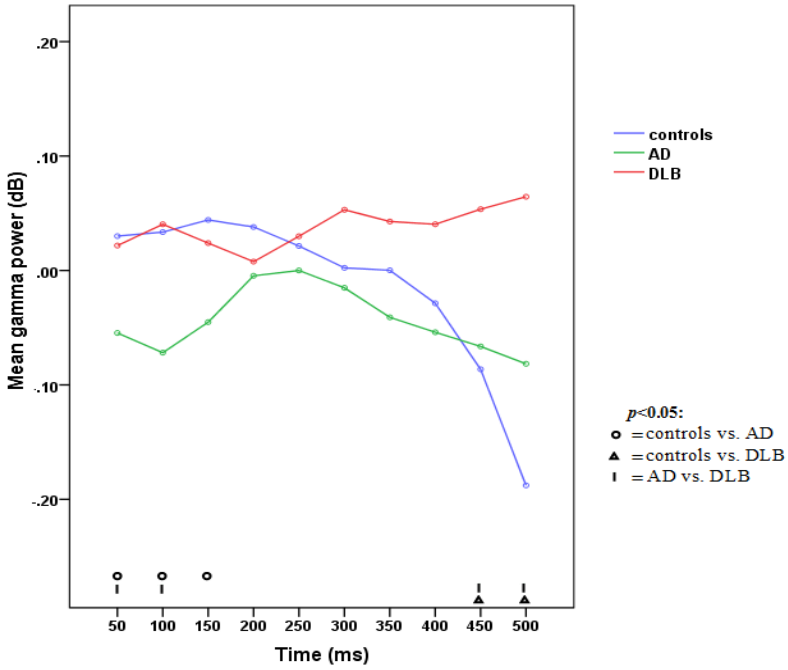


Figure 7.18. Mean gamma power (dB) associated with the executive conflict effect for the post-target 500 ms interval for each group, averaged across all regions. The time points at which significant differences (p <0.05) between groups occurred are depicted on the plots (after correcting for multiple comparisons using Bonferroni correction).

Executive conflict effect summary

- The ERSP associated with the executive conflict effect primarily comprised ERS and ERD which was diffuse across the time and frequency domains.
- Across all frequencies, the executive conflict effect ERSP was highly variable with respect to time (and of relatively little power compared to the ERSP associated with the target conditions).
- In the gamma range there were group differences in the ERSP with respect to time (independent of region). In the low gamma interval there was a lack of reactivity in the AD group relative to the controls. In the higher gamma interval, the group differences were primarily due to a lack of reactivity in the DLB group at various time points.

Chapter 8 . Oscillatory reactivity of the attentional networks in DLB: discussion

The objective of the time-frequency analyses, reported in chapters 5-7, was to characterise the oscillatory reactivity associated with the modified ANT cue and target stimuli, and to deduce the extent to which this reactivity differed in the dementia groups relative to the controls. The attentional network analyses (chapter 7) clarified the oscillatory reactivity associated with each of the networks, and highlighted aberrant reactivity in the DLB group. Understanding the aetiology of this DLB group atypical reactivity has potential to provide insight into the pathophysiology underlying the attentional dysfunction associated with the condition.

8.1 Cue and target oscillatory reactivity

From the results reported in chapter 6, it is evident that across all of the task conditions there was a consistent trend with respect to group differences in the ERSP. Following the presentation of a stimulus (cue or target) the DLB group showed a profound lack of oscillatory reactivity, evident across the majority of regions of interest, which was most apparent in the lower frequencies (< 30 Hz). A lack of ERS in the theta range, demonstrable in all regions across the majority of the 500 ms interval of interest, was particularly characteristic of the DLB group. The DLB ERSP was broadly similar following the presentation of the cues and targets, indicative of the DLB group exhibiting diminished oscillatory reactivity in response to the stimuli irrespective of the content. In contrast to the DLB group, the oscillatory reactivity of the AD group was more comparable to that of the control group, particularly following the presentation of a cue. For the cue conditions, the atypical activity in the AD group was not confined to a specific frequency range, but appeared region specific, with a lack of reactivity most evident over the left parietal region. This chimes with the evidence in AD that there is temporo-parietal hypoperfusion particularly in the left tempero-parietal region (Cappa et al., 2001), and amyloid appears to have a predilection for deposition in the parietal cortex (Klunk et al., 2004; Ossenkoppele et al., 2012). Relative to the cue reactivity, the AD group exhibited reduced oscillatory reactivity

across a greater number of regions following the presentation of a target, particularly the incongruent target (with a lack of theta ERS across the majority of regions). These findings indicate that the atypical oscillatory reactivity in the AD group is primarily associated with processing stimuli which require higher order cognitive processing (as there is an element of executive functioning involved), which fits with the extensive literature documenting executive impairment in AD patients (Baudic et al., 2006; McGuinness et al., 2010), and is in tune with the behavioural deficits in executive function shown in the AD group as presented in chapters 3 and 7.

When comparing the two dementia groups it is apparent that in the DLB group aberrant activity was much more diffuse across the regions relative to the AD group, and largely indiscriminate with respect to stimulus content. The diminished global oscillatory reactivity in the DLB group, most prominent in the theta range, is suggestive of a reduced ability to synchronise and desynchronise oscillatory activity in response to visual stimuli. As the DLB reactivity was comparable for the cue and target conditions (and all analyses were conducted using correct response trials), this suggests that the diminished reactivity in the DLB group in response to the cues was not merely due to a lack of understanding/processing of the cue content; rather it is an expression of an overall less efficient modulation of oscillatory activity in response to external stimuli. It has been suggested that global theta ERS elicited during visual attention tasks (in the initial 500 ms post-stimulus presentation) may be an electrophysiological correlate of allocation of attention to stimuli, and has a role in integrating visual information for further cognitive processing (Missonnier et al., 2006a). The attenuated theta ERS in DLB patients may therefore reflect reduced allocation of attention to external stimuli.

The thalamocortical system has a pivotal role in the generation of cortical synchronous oscillatory activity (Timofeev et al., 2012), the frequency of which is dependent upon current brain state and mental activity. It is feasible that reduced integrity of this system in DLB could be a contributory mechanism underlying the lack of oscillatory change, particularly theta ERS, in the DLB group. As discussed in chapter 1 (section 1.4.2), the activity of non-specific thalamocortical afferents projecting to the superficial cortical pyramidal cells are the main source of the scalp EEG signal (Kirschstein & Kohling, 2009). From surface EEG recordings it is therefore difficult to delineate the extent to which specific structures, particularly subcortical structures, contribute to the signal. Whilst oscillatory

activity of the thalamus has been found to regulate cortical oscillatory synchronisation (Malekmohammadi et al., 2015), this involves a complex interplay between lower and higher frequency activity, and hence it is difficult to deduce the extent to which activity of the thalamus contributes to the theta ERS recorded at the scalp. However, given the extensive literature documenting thalamic abnormalities in DLB including: increased thalamic perfusion (O'Brien et al., 2005), reduced fractional anisotropy (Watson et al., 2012), and microstructural damage in thalamic regions projecting to the parieto-occipital and pre-frontal cortices (Delli Pizzi et al., 2014b), it would be reasonable to speculate that thalamic pathology may be contributory factor underlying the lack of reactivity in DLB. However, in order to elucidate the extent to which thalamic abnormalities contributed to the diminished global reactivity in the DLB group, further analyses, e.g. source localisation analyses, would be necessary.

Furthermore, given that global thalamocortical oscillatory activity is generated from both long-range and localised oscillatory synchronisation (Timofeev et al., 2012), it is possible that functional connectivity deficits may contribute to the manifestation of aberrant oscillatory reactivity. In particular, a resting state fMRI study conducted by Peraza et al. (2015), based on the CATFieLD participant cohort, demonstrated that long-range functional connectivity was reduced in DLB patients relative to AD patients. Whist it is possible that this disruption in long-range connectivity may contribute to the global lack of reactivity in the DLB patients, it is not clear how this translates to reactivity of the specific frequency bands. Cross-modal comparisons of functional imaging against the EEG data in the same patients in the CATFieLD cohort may provide further elucidation.

In the no cue condition group differences were evident in the alpha and gamma frequency bands, and were primarily due to less ERD in the DLB group relative to the controls (evident across several regions), although there was less ERD in the AD group relative to the controls in the left parietal region. Given that the no cue condition denotes the absence of a stimulus, the oscillatory reactivity associated with the no cue condition could be considered to be an indicator of anticipatory attention (as it precedes the onset of the target). ERD in the alpha band, particularly in posterior regions, has been found to be associated with anticipatory attention for an upcoming stimulus (Klimesch, 1999; Thut, 2006). It is therefore possible that the reduced alpha reactivity in the DLBs in the absence of a stimulus, which has previously been reported in LBD patients relative to controls (Franciotti et al., 2006), may be a sign of diminished anticipatory attention for the upcoming target.

The behavioural data (chapters 3 and 6) showed that the mean RTs associated with the cue conditions were faster for the control group relative to the dementia groups, but there was no difference in cue mean RTs between the dementia groups. Whilst the DLB group clearly showed more profound diminished cue reactivity in terms of the EEG relative to the AD group, behaviourally the groups were comparable, and there were no associations between the lack of DLB reactivity and mean RTs. It is possible that this is explicable in terms of different mechanisms underlying the oscillatory reactivity and mean RTs. The reactivity reflects very early visual processing of the stimuli and allocation of attention, whereas the RTs also incorporate implementation of a motor response to the target; a factor which was evident given the association between motor severity (as measured on the UPDRS) and overall mean RT in the LBD group (see chapter 3).

With regard to the target behavioural data, the controls exhibited faster mean RTs relative to the dementia groups for both target conditions. There was no difference between the dementia groups for the incongruent target mean RTs, however the AD group congruent target mean RT was faster than that of the DLB group. Given that DLB reactivity was broadly similar for both target conditions, yet AD group aberrant reactivity was more evident for the incongruent target, it is possible that the atypical reactivity in AD patients during incongruent trials accounts for the more pronounced RT slowing with increasing target difficulty in the AD group (relative to the RT slowing of the DLB group).

To summarise, from the cue and target ERSP analyses it is clear that in the DLB group there was a profound lack of global reactivity in stimulus-present conditions, which was most evident in the lower frequency range, particularly theta. Whilst possible explanations regarding the pathophysiology underlying this attenuated reactivity have been discussed in the paragraphs above, the results of the ERSP attentional network analyses (discussed in section 8.2) provide greater insight into this atypical reactivity in the context of attentional dysfunction.

8.2 Attentional network oscillatory reactivity

This section discusses the results of the attentional network analyses (alerting, orienting, and executive conflict) reported in chapter 7.

8.2.1 Alerting

The oscillatory reactivity associated with the alerting effect in the control group included theta ERS spanning the 500 ms interval, which peaked at approximately 300 ms. There was also alpha ERSP which comprised an initial ERS over the occipital and bilateral central regions, followed by an ERD evident across the vast majority of the regions from approximately 250 ms. Global beta ERD was also evident from approximately 200-250 ms. In the gamma range, there was much greater ERSP variability across the 500 ms interval relative to the lower frequencies across all regions, as well as less overall ERSP power.

The DLB group showed a lack of alerting oscillatory reactivity which was most apparent in the lower frequencies of interest (< 30 Hz). DLB patients exhibited a lack of global ERS (across all scalp regions) in the theta range, evident across the majority of the 500 ms interval; this ERS was attenuated relative to both the AD and control groups, and thus was characteristic of the DLB group. Occipital beta ERD in the DLB group, in the latter half of the 500 ms, was also less than that of the control and AD groups. In comparison, the only alerting difference between the AD and control groups was less beta ERD in the AD group in the left central and left parietal regions. It is therefore apparent that the aberrant oscillatory reactivity associated with the alerting network was primarily characteristic of the DLB group.

The behavioural data (chapter 3) showed that the alerting effect was not significant in either of the dementia groups; however when the groups were compared in terms of the alerting effect magnitude there were no group differences (likely due to the greater alerting effect standard deviation in the dementia groups relative to the controls). In an fMRI study of the attentional networks, Firbank et al. (2015) also reported an absence of a behavioural alerting effect in the dementia groups, which would be expected given that it was based on the CATFieLD participant cohort. In terms of functional network activations, this study demonstrated that there were no group differences regarding activations associated with the alerting effect; all groups showed comparable activation in fronto-parietal- occipital regions, similar to previous ANT studies such as Fan et al. (2005). The comparable magnitude of the behavioural alerting effect in all three groups, and lack of alerting activation group differences, is in stark contrast to the lack of oscillatory reactivity in the DLB group. There were no associations between the DLB behavioural alerting effect and attenuated oscillatory reactivity, supporting the notion that the behavioural and ERSP analyses may probe different mechanistic aspects (as discussed in section 8.2.1). Thus these findings indicate that ERSP

analyses may capture alerting associated deficits not evident from imaging analyses techniques, and suggest that the reduced ability to maintain an alert state in DLB patients may be explicable in terms of global dysfunction of low frequency neuronal reactivity which, as noted above, may be driven by global changes such as alterations in cortic-thalamic drive.

The alerting network is purported to be to be modulated by noradrenergic projections from the locus coeruleus (Coull et al., 2001; Raz, 2004). Given that DLB patients have been found to have a paucity of noradrenergic neurons in the locus coeruleus (Szot et al., 2006), and neuronal activity of the locus coeruleus has been found to have a modulatory role on bilateral oscillatory activity associated with arousal (Berridge & Waterhouse, 2003), reduced integrity of the locus coeruleus noradrenergic system may be a contributory factor underlying the diminished alerting reactivity in DLB. The association between noradrenergic function and cognition in LBD is not well documented, however there is preliminary evidence to suggest that Atomoxetine (a selective norepinephrine reuptake inhibitor) may improve cognitive functioning in non-demented Parkinson's disease (PD) patients with mild cognitive impairment (Aarsland et al., 2012). Specifically, in PD patients Atomoxetine has been shown to lead to improvements in executive function (Marsh et al., 2009) and global cognitive functioning (Weintraub et al., 2010), as well as enhanced verbal fluency associated with increased functional connectivity between the right inferior frontal gyrus and dorsolateral prefrontal cortex (Borchert et al., 2016). It would therefore be of interest to investigate whether noradrenergic medication alleviates attentional dysfunction in LBD patients, and in particular whether this modulates aberrant alerting reactivity.

For the alerting effect, the ability to maintain an alert state, the activity associated with this network is representative of the contrast in the activity between anticipatory attention (in the absence of a stimulus) and attending to an external visual stimulus (the neutral cue). It is possible therefore that the lack of reactivity in the DLB group may be associated with reduced efficiency of switching between a state of anticipatory attention and attending to the external environment (a visual stimulus). The presentation of cues prior to the onset of target stimuli has been shown to result in deactivation of the default mode network (DMN), with a switch to salience networks (Sidlauskaite et al., 2014). It is therefore possible that atypical DMN deactivation may contribute to the lack of reactivity associated with the alerting effect in DLB. Firbank et al. (2015) investigated DMN deactivation in the CATFieLD group following cue presentation (neutral and spatial) relative to the no cue condition and found the control

group exhibited significant parietal deactivation for both cue conditions, as well as frontal deactivation to the neutral cue. However, the LBD group exhibited only frontal deactivation following the neutral cue. These findings suggest that in the LBD group there was a failure to deactivate parietal regions during cue-present conditions, and thus this lack of parietal deactivation following the neutral cue relative to the no cue may be a contributory factor in the lack of alerting reactivity in DLB. The findings of the cue oscillatory reactivity (discussed in section 8.1) showed that whilst the DLB group did exhibit some atypical activity in the no cue condition, the lack of reactivity was much more profound in the cue-present (and target) conditions. The lack of alerting reactivity in the DLB group is therefore likely to be explicable in terms of lack of reactivity in response to attending to a visual stimulus (the neutral cue), as opposed to atypical activity associated with the no cue condition which, in turn, may indicate reduced efficiency in attending to and processing the neutral cue, possibly due to a less efficient DMN deactivation during the presentation of visual stimuli.

8.2.1.2 Clinical correlates of alerting ERSP in DLB

Theta reactivity

For the DLB group alerting effect, a lack of theta ERS over the right parietal region between 200-450 ms was associated with greater severity of clinically assessed cognitive fluctuations (as measured by the total CAF score). Fan et al. (2005) found the alerting network to be associated with activation of the thalamus, frontal and parietal regions, with the right parietal lobe being a key region in this network (Galvao-Carmona et al., 2014) . Patients with parietal lesions, particularly in the right hemisphere, have been found to have a reduced ability to maintain an alert state (Sturm & Willmes, 2001), indicative of this region having a crucial role in the maintenance of attention. The parietal lobe is known to be markedly affected in DLB patients, for example, hypoperfusion of parietal cerebral blood flow has been demonstrated in individuals with DLB (Colloby et al., 2002). Furthermore, there is evidence to suggest that the right hemisphere parietal lobe may be particularly affected, with cortical thinning of the right-temperoparietal junction (Blanc et al., 2015) and the right superior parietal lobule (Delli Pizzi et al., 2014a) being observed in DLB patients. In addition, it is possible that the attenuated theta ERS in this region may be due to activity of afferent projections from right thalamus, as cholinergic imbalance (tCho/tCr increase) within the right thalamus has been found to correlate with the severity of cognitive fluctuations in DLB

patients (Delli Pizzi et al., 2014b). The findings support the hypothesis that cognitive fluctuation severity would be associated with low frequency activity, as reported in previous literature (Bonanni et al., 2008; Walker et al., 2000c), and are suggestive of attenuated theta reactivity in the right parietal region being a key factor underlying the pathophysiology of cognitive fluctuations in DLB.

In the DLB group, lack of alerting effect theta ERS in the bilateral frontal, right parietal and occipital regions (in the specified time intervals which differentiated the DLB theta from the AD and control groups) was associated with lower MMSE and CAMCOG scores. This is indicative of an association between absence of theta synchronisation and reduced global cognitive functioning; the fact that this association was evident across several regions suggests that this is a robust finding. This also fits with existing literature showing that theta synchronisation has a crucial modulatory role in cognitive functioning, in particular working memory (Klimesch, 1999), as well as attentional control (Luu et al., 2004) and spatial attention (Frey et al., 2015). Furthermore, it has been suggested that attenuated theta ERS during visual tasks may be predictive of cognitive decline. Missonnier et al. (2006b) conducted a longitudinal study of 24 mild cognitive impairment (MCI) patients (aged 73-93 years old) in which participants completed the n-back working memory task and theta ERS was analysed, and participants were subsequently followed up after one year to assess MCI status. Upon follow up, 13 of the patients were classified as progressive MCI, whilst the other 11 were deemed to have stable MCI. The progressive MCI group had shown reduced theta ERS globally, in the 500 ms post stimulus (for all stimulus conditions), relative to the stable MCI group. The authors suggested that this attenuated theta ERS may have been the result of dysfunction of attention-related neural networks.

Beta reactivity

In the DLB group diminished beta ERD (relative to the controls), evident in the latter half of the 500 ms interval in the right frontal and left central regions, was associated with a higher UPDRS total score (motor subsection, described in chapter 2- section 2.3.4). This indicates that attenuated beta ERD was associated with greater motor impairment severity in DLB patients. In attention tasks requiring a motor response, beta ERD following cueing stimuli has been found to be related to cognitive processing in preparation for a motor

response (Kaiser et al., 2001), and therefore the beta ERD in the DLB patients may reflect reduced cognitive processing in preparation for the target response.

8.2.2 Orienting

The orienting effect was characterised primarily by ERS which was diffuse across both the time and frequency domains, although there was a clear theta ERD peaking between 200-300 ms (across all regions) evident in all of the groups. In the gamma band there was a gradual ERD with increasing time which peaked between 350-400 ms. There were no overall group differences regarding the oscillatory reactivity associated with the orienting network (for any of the frequency bands studied), which was in alignment with the orienting effect behavioural data which also demonstrated no group differences. From a functional imaging perspective, Firbank et al. (2015) also found all three groups to be comparable in terms of the orienting effect; there were no significant fMRI activation increases associated with the orienting effect for any of the groups in this study.

With regard to the reactivity associated with the neutral and spatial cue conditions (used to calculate the orienting effect), as discussed in section 8.1, the DLB patients exhibited a profound lack of global low frequency reactivity which was broadly comparable for both of the cue conditions. Relative to the DLB patients, the AD group exhibited much less atypical reactivity, and this was more localised, but like the DLB group the aberrant activity was similar for both cue conditions. Therefore whilst all three groups showed similar disparity in the reactivity associated with the two cue conditions (hence the comparable orienting effect across the groups), the underlying reactivity used to calculate this effect was substantially different between the groups. Aberrant reactivity in the DLB group was more evident in stimulus-present conditions relative to the no cue condition, and therefore this explains the seemingly typical DLB orienting reactivity (the difference between two stimulus-present conditions), in contrast to the diminished DLB alerting reactivity (no cue versus cue-present).

The power of the orienting reactivity (across all three groups) was diminished relative to the alerting effect, and relative to the reactivity associated with the neutral and spatial cues used to calculate it. Along with the lack of orienting activation demonstrated by Firbank et al. (2015), this indicates that the orienting effect was relatively subtle. Deiber et al. (2013) found that orienting was associated with an alpha ERD in posterior brain regions which attenuated

with age, and therefore the overall lack of orienting reactivity in our participants is unsurprising and may be explicable in terms of the age of the cohort.

The orienting network has been suggested to be modulated by the basal forebrain cholinergic system (Fan, 2005), which is markedly affected in DLB patients (Clerici et al., 2007; Grothe et al., 2014). Given that cholinergic imbalance in the thalami has been found to correlate with cognitive fluctuation severity in DLB (Delli Pizzi et al., 2014a), it was hypothesised that there would be associations between aberrant orienting reactivity in the DLB group and cognitive fluctuation severity, however this hypothesis was not supported. Although the vast majority of the dementia patients were taking cholinesterase inhibitors (as discussed in chapter 5), and cholinergic agonists have been found to modulate low frequency oscillatory activity (Bauer et al., 2012), it is unlikely that cholinergic medication usage accounts for the absence of group differences in orienting reactivity as the patients would still have profound cholinergic deficits. Furthermore, medication usage was considered as a covariate during the attentional network analyses, however there were no significant medication effects on the attentional network findings. It is possible that the orienting network may be less sensitive to cholinergic processes than has been previously suggested, rather it may be that tasks which require a high degree of re-orienting, such as an invalid cueing task (Vossel et al., 2006), might be more sensitive to cholinergic deficits in DLB, however further work would be needed to clarify this.

8.2.3 Executive conflict

The oscillatory activity associated with the executive effect comprised intervals of ERS and ERD, across all frequencies, which were diffuse across both the time and frequency domains. Group differences were only evident in the gamma range; time x group interactions, independent of region, were evident in both the 30-45 Hz and 55-90 Hz gamma intervals. In the low gamma range (30-45 Hz) there was a lack of reactivity in the AD group relative to controls at 50 and 500 ms, whilst the group x time interaction in the higher gamma range (55-90 Hz) was due to greater ERD in the AD group relative to controls in the initial 150 ms, and a lack of DLB ERD relative to the control and AD groups between 450-500 ms.

The behavioural data showed that the executive conflict effect was greater in both of the dementia groups relative to the controls (but there was no difference between the dementia

groups), indicative of reduced conflict processing efficiency in the dementia patients. In chapter 3 it was shown that the AD group had a greater error rate for incongruent trials relative to the controls, whilst the LBD group had greater error rates for both congruent and incongruent target conditions relative to the controls. However, in the dementia groups there were no associations between the atypical gamma reactivity and this behavioural data (mean RT or error rates). Whilst gamma synchronisation has been shown to be associated with executive functioning (Bosman et al., 2014), the group differences in gamma reactivity (reported in chapter 7) were minimal. Given that Deiber et al. (2013) found that beta band reactivity associated with the executive conflict effect was temporally delayed in elderly individuals relative to younger individuals, and my analyses only considered the activity in the initial 500 ms post-stimulus interval, it is feasible that the executive effect beta reactivity (and potential group differences and behavioural correlates) may not have been captured in the present study (please see section 8.4 for further discussion). However, the broadly comparable executive conflict reactivity across the groups (with the exception of the minimal gamma differences) is consistent with the functional activation findings of Firbank et al. (2015), where all three groups exhibited similar fronto-parietal and lateral occipital activation associated with the executive network. The authors suggested that this indicated that the dementia groups employed the same distributed executive network as the controls.

From the results discussed in sections 8.1 and 8.2, overall it is apparent that group differences were most evident in the reactivity associated with the presentation of the cue and target stimuli, as opposed to the attentional network effects (i.e. the absolute ERSP values as opposed to the relative differences between the ERSP values). Therefore, although the oscillatory reactivity associated with the orienting and executive effects was fairly comparable across the groups (suggestive of comparable network efficiency), there were clear group differences in the reactivity for the task conditions used to calculate these network effects, primarily due to a lack of absolute reactivity in the DLB group. This fits with findings of the behavioural data; group differences were most evident in the RTs corresponding to each cue and target condition (faster RTs in the controls relative to the dementia groups), as opposed to the RT benefits or costs associated with each of the attentional network effects. This highlights the importance of interpreting the attentional network reactivity in conjunction with the absolute reactivity for each task condition.

8.3 Comparison with other ANT studies

As discussed in chapter 5, to date few studies have investigated the oscillatory reactivity associated with the ANT (Deiber et al., 2013; Fan et al., 2007). It is difficult to make direct comparisons between my results and the findings of these studies, as there is substantial heterogeneity with respect to the participant cohorts, design of the task, and the analyses methods used. Fan et al. (2007) found that in a cohort of young healthy participants the alerting network was associated with a decrease in theta, alpha and beta activity between 200-450 ms post-stimulus (across the majority of regions of interest). Whist the alerting effect results discussed in this chapter were comparable to Fan et al. (2007) for the alpha and beta range, my results demonstrated an ERS in the theta range as opposed to an ERD. There were also substantial differences between my results and those reported by Fan et al. (2007) for the orienting and executive effects; it is likely that this is due to disparities in the task design, the participant cohorts, and the analyses methods. For example, Fan et al (2007) used dipole modelling in order to determine the regions of interest. In the Deiber et al. (2013) study, the task design was considerably different from our modified ANT; relative to our task there was a much longer cue duration (400 ms), as well as a longer-cue target interval, and they used a pre-cue baseline interval for both the cue and target analyses which was of much longer duration (800 ms) than my baseline interval (250 ms). Despite these methodological differences, Deiber et al. (2013) reported oscillatory reactivity (between 4-30 Hz) for an elderly cohort (across each task condition) which was broadly comparable in the 500 ms interval of interest to the reactivity of our controls; a broad theta ERS, and alpha and beta ERD in the latter half of the 500 ms interval. As the oscillatory reactivity elicited by our modified ANT is similar to the reactivity previously shown in elderly individuals, this is suggestive of our task being suitable for investigating attentional network reactivity in older and cognitively compromised cohorts. However, given the overall variability in the observed attentional network oscillatory reactivity with fairly subtle methodological differences between studies, this suggests that ERSP data needs to be interpreted in the context of the study in which the data was recorded (i.e. the data should be considered in the context of the specific study cohort and analyses techniques used).

8.4 Limitations

Despite careful deliberation to ensure that the time-frequency analyses parameters were appropriate for the data, inevitably there were several constraints associated with the analysis methodology. There is little consensus in the EEG literature regarding the optimal parameters for time-frequency analyses, consequently the wavelet analysis design was largely driven by the data. As discussed in the methods section, due to the cue-target SOA (stimulus onset asynchrony) the post-cue 500 ms was deemed to be the maximum feasible time interval in which the ERSP could be investigated. For the target conditions, incorporating activity beyond this 500 ms interval in the analyses would result in the motor response being present for some of the participants (mainly the controls), and for fast-responders any activity seen could be due to the presentation of a cue related to the next trial.

Across all task conditions, the global ERS theta peaks in the DLB group tended to follow the same time course as the controls but were attenuated in power. This suggests that the lack of theta reactivity in the DLB group was not due a failure to capture the reactivity in the 500 ms interval (i.e. slowing of DLB theta reactivity in the temporal domain). However, given that across all task conditions (and all groups) beta ERD began in the latter half of the 500 ms interval, it is possible that group differences in beta ERD would have been evident had it have been feasible to conduct the analyses using longer post-stimulus (cue and target) time windows. Given that the time course of beta ERD is related to cognitive processes involved in motor response preparation (Kaiser et al., 2001), it is possible that the diminished beta ERD in the DLB group (evident across all task conditions across the majority of regions) could be due to delayed motor response preparation. The association between the alerting effect lack of beta ERD and motor impairment severity in right frontal and left central regions suggests that this potential delay in motor response preparation is particularly pertinent for the bradykinetic DLB patients. Furthermore, from the data it is not possible to determine the direction of causality; the slowed/lack of beta ERD in the DLB group could cause a slowed motor response preparation, or vice versa the slowed/lack of beta ERD could be the result of a slowed motor response preparation. Despite this limitation, it is evident from the data that the DLB group exhibited diminished early beta reactivity (for both cue and target conditions) suggestive of deficits in early motor response preparation.

As discussed in section 8.2, overall there was a lack of association between the attentional network reactivity and behavioural data (mean reaction times and error rates). It is

possible that these behavioural parameters may be more closely aligned to response-locked oscillatory reactivity (as opposed to stimulus-locked reactivity). Whilst response-locked analyses are a potential option for further investigation, the limitations of this approach are comparable to the target-locked analyses; notably that for fast-responders the activity could be due to the cue onset for the following trial.

An additional limitation concerns the selection of the most appropriate frequency band intervals used in the statistical analyses. Comparable to Fan et al. (2007) fixed frequency bands were used, but in addition the individual alpha frequency (IAF) was also calculated. Whilst there was some heterogeneity regarding the group differences pertaining to alpha reactivity when using the two methods, this is to be expected given that the alpha band interval was shifted with the IAF to ensure that participants' maximum alpha reactivity was captured. However there were consistencies between the two methods in terms of reactivity differences between groups; in particular group differences for the post-target alpha were fairly comparable when using either fixed alpha or IAF. This indicates that the findings, primarily of reduced alpha reactivity in the DLB group (across several regions) are robust, suggesting that this absence of DLB ERD is not merely due to a failure to capture the peak alpha activity in the DLB group.

With regard to the statistical analysis methodology, a potential limitation concerns the analysis of the gamma band activity. Across all task conditions the vast majority of the significant group differences were evident in the lower frequencies. However from the time-frequency plots there were apparent group differences in the gamma range (mainly a lack of ERD in the DLB group), yet overall there were few significant group differences in this frequency range. In the time domain, 50 ms intervals were used to analyse the activity and from the mean time-frequency plots it is apparent that this interval was sufficient to capture the activity of interest (across all frequencies). However it is possible that many of the apparent group differences were not significant because of a failure to find differences due to the broad gamma intervals (in the frequency domain) used (30-45 Hz and 55-90 Hz) for the analyses. An alternative approach would be to use the mean time-frequency plots to select the areas of apparent ERD/ERS in the gamma range, and conduct the group analyses for the activity in these selected gamma intervals. This technique could potentially be used in future analyses to clarify whether the lack of significant group differences in the gamma band was indeed due to the groups having comparable oscillatory reactivity in this frequency range, as

opposed to a failure to capture this activity. A difficulty with this proposed technique however is that it would be challenging to define the boundaries of the gamma intervals due to the intermittent nature of the activity in this range. Therefore the method used for the gamma analyses reported in this thesis was chosen as it was the more objective approach of the two methods.

A final potential limitation concerns the subtraction technique used to calculate the oscillatory reactivity of the attentional networks; it has been suggested that this simple contrast technique is unlikely to isolate complex cognitive processes such as space and time orienting (Deiber et al., 2013). For each of the task conditions used in the network calculations, the cognitive mechanisms and number of resources required for each condition differs substantially (Galvao-Carmona et al., 2014). For example, the no cue condition denotes anticipatory attention for an unknown upcoming stimulus (either cue or target), whereas in the cue-present conditions it is known that the upcoming stimulus will be a target. It has therefore been suggested that the no cue condition involves greater cognitive load relative to the neutral cue condition, and thus the alerting effect is not simply a contrast between an alert and not alert state; it involves more complex cognitive processes (Galvao-Carmona et al., 2014). Whilst the limitations of this contrast method are acknowledged, this is the standard network calculation technique which has been used across studies enabling characterisation of the attentional networks in conjunction with the behavioural network effects in both EEG (Deiber et al., 2013; Fan et al., 2007; Neuhaus et al., 2010) and fMRI (Fan et al., 2007; Fan et al., 2005). The simplicity of the technique enabled the comparison of the attentional network oscillatory activity with the behavioural data (calculated using the same technique).

8.5 Summary

In summary, following the presentation of the cue and target stimuli the DLB group exhibited a profound lack of oscillatory reactivity in the lower frequencies (<30 Hz), irrespective of stimulus condition. Aberrant reactivity in the DLB group was more pronounced in stimulus-present conditions relative to the no cue condition, and thus it is postulated that this reflects reduced efficiency at processing visual stimuli for further cognitive processing, possibly due to reduced integrity of the cortico-thalamic system. This profound lack of reactivity may be a useful biomarker for DLB (e.g. for diagnostic purposes)

and thus is worth investigating further from this perspective. With regard to the attentional network reactivity, oscillatory reactivity associated with the orienting and executive networks was fairly comparable across all groups; primarily intermittent ERS and ERD, of reduced power relative to the alerting network, diffuse across the time and frequency domains in all regions. For the alerting network, the DLB group exhibited attenuated reactivity in the lower frequencies (< 30 Hz); in particular a lack of global theta ERS. Attenuated global oscillatory reactivity in the DLB group specific to the alerting network is indicative of this fractionated aspect of attention, the ability to maintain an alert state, being differentially affected in the DLB group relative to the AD and control groups. Lack of DLB ERS between 250-450 ms over the right parietal region associated with greater cognitive fluctuation severity, and thus aberrant theta reactivity of this region may contribute to the underlying pathophysiology of cognitive fluctuations in DLB.

Chapter 9 . Conclusions

The objective of this PhD project was to use a modified version of the ANT in conjunction with simultaneous EEG recordings in order to delineate which fractionated aspects of attention are affected in LBD, and the underlying pathophysiology associated with these attentional impairments. This study is the first to investigate the electrophysiology of the attentional networks in a cohort of LBD patients, and thus is a crucial step towards understanding the pathophysiology of the attentional dysfunction associated with the condition. Knowledge of the underlying neurophysiology of attentional dysfunction is essential in order to develop more effective management strategies for this clinical feature.

9.1 Summary of findings

As discussed throughout this thesis, analysis of the ANT data was approached from two perspectives: behavioural (reaction time) analyses, and EEG time-frequency (ERSP) analyses.

9.1.1 Behavioural analyses

Despite various modifications of our task design relative to the original ANT (described in chapter 2), the modified ANT elicited significant alerting, orienting, and executive conflict effects in a cohort of young healthy individuals. Comparable to the findings reported by Fan et al. (2002), the attentional network effects observed in the young healthy cohort were uncorrelated, suggestive of independence of the attentional networks in young healthy adults. It is therefore reasonable to conclude that our modified ANT is a valid version of the original task. Furthermore, across the whole age range of healthy participants (ranging from 17-94 years old), the modified ANT elicited significant alerting, orienting and executive conflict network effects, indicative of our modified ANT being valid across a vast age range of healthy individuals.

The behavioural analyses of the dementia groups (AD and LBD) and age-matched healthy controls showed that with regard to overall mean RT (across all task conditions) the dementia groups were slower than the controls. However, the LBD group were also slower

than the AD group. This fits with existing literature demonstrating RT slowing in LBD patients relative to age-matched controls and AD patients (Ballard et al., 2001; Ballard et. al, 2002; Fuentes et al., 2010). It is likely that motor impairment was a significant contributory factor in the LBD slowing, as increased overall mean RT in this group was associated with a higher UPDRS total score.

With regard to the attentional networks, an alerting effect, associated with the ability to maintain an alert state, was evident in the control group, but this was not significant in either of the dementia groups. This is indicative of reduced efficiency of the alerting network in the dementia patients. In an fMRI study of the CATFieLD participant cohort, Firbank et al. (2015) found all groups (LBD, AD, controls) to have comparable fronto-parietal-occipital activations associated with alerting effect; this suggests that the lack of a behavioural alerting effect in the dementia groups is unlikely to be due to region-specific functional deficits of the alerting network. Other global factors reducing alerting efficiency may be apposite. For example, the noradrenergic system is postulated to have a modulatory role on the alerting network (Fan et al., 2005), therefore it is possible that reduced noradrenergic system integrity may be a contributory factor in the dementia groups.

With regard to the orienting effect, which is associated with the selection of information from sensory input, there were no group differences. The orienting effect in the AD group was comparable to previous literature showing preservation of the orienting network in AD patients (Fernandez-Duque & Black, 2006). Given that the orienting network is postulated to be modulated by the basal forebrain cholinergic system (Fan, 2005), which is markedly affected in DLB patients (Clerici et al., 2007; Grothe et al., 2014), I hypothesised that the LBD group would exhibit reduced orienting efficiency, however this conjecture was not supported by my subsequent research findings. Whilst it is possible that this may, in part, be due to cholinesterase inhibitor usage in the LBD patients, when medication usage was controlled for in the analyses models there were no effects of the use of these medications on the findings. The findings are therefore suggestive of preservation of the orienting network in LBD. Evidence for cholinergic effects on orienting primarily come from non-human primate drug studies, in which drugs that influence acetylcholine affected orienting but not alerting efficiency (Davidson et al., 1999). These studies had relatively short cue-target intervals compared to our study, and in addition the modified ANT only used 100 % valid peripheral cues; this, with the longer time delay between cue and target in the modified ANT, enhances

the likelihood of voluntary orienting, and it is not known what influence cholinergic function would have on this. Clearly this is an area lacking clarity, although interestingly a recent report examining the effect of scopolamine on the ANT, both behaviourally and from a functional imaging perspective, suggested that cholinergic antagonism has widespread effects across all components of the ANT leading to a general slowing, but in particular slowing in response to presentation of the incongruent target (Thienel et al., 2009). This finding aligns with the findings of particular deficits in incongruent trials in our dementia groups from a fMRI activation perspective (Firbank et. al, 2015).

A significant executive conflict effect was observed in all three groups. The magnitude of this executive conflict effect was greater in both of the dementia groups relative to the controls; this is indicative of the dementia patients exhibiting reduced ability to resolve conflict amongst responses (irrespective of dementia type). These findings fit with the existing ANT literature demonstrating reduced efficiency of the executive conflict network in AD patients (Fernandez-Duque & Black, 2006). In addition, executive dysfunction has been shown to be characteristic of LBD patients (Noe et al., 2004). Given that the dopaminergic system is postulated to have a regulatory role on the executive conflict network (Fan et al., 2005), the reduced executive conflict efficiency in the LBD patients fits with the notion of dopaminergic mediated frontal-striatal dysfunction being a contributory factor to the executive dysfunction in LBD (Kehagia et al., 2013). However, as noted above, there is also probably a significant role of cholinergic dysfunction as well.

9.1.2 EEG time-frequency analyses

From behavioural data alone it is difficult to delineate the neurophysiological mechanisms underlying the attentional network effects, hence the acquisition of simultaneous EEG recordings whilst the participants completed the task. Comprehensive time-frequency analyses, described in chapters 4-8, were conducted in order to determine the oscillatory reactivity associated with each of the attentional networks, and to investigate whether the DLB group exhibited disease specific aberrant reactivity.

Following presentation of the ANT stimuli (cue and target), the DLB group exhibited a profound lack of oscillatory reactivity irrespective of stimulus content. This lack of reactivity was evident across the majority of regions of interest, and was most apparent in the

frequencies below 30 Hz. Lack of global theta ERS, spanning the 500 ms post-stimulus interval, was particularly characteristic of the DLB patients. Global theta ERS elicited during visual attention tasks is postulated to have a crucial role in the allocation of attention and integration of visual information for further cognitive processing (Missonnier et al., 2006a), and thus the absence of theta ERS in DLB may reflect reduced allocation of attention to external stimuli. Given the thalamo-cortical system has a pivotal role in generating cortical synchronous oscillatory activity (Timofeev et al., 2012), and the extensive literature demonstrating thalamic abnormalities in DLB patients (O'Brien et al., 2005; Watson et al., 2012), as well as microstructural damage in thalamic regions projecting to the parieto-occipital and pre-frontal cortices (Delli Pizzi et al., 2014b), it is speculated that reduced integrity of the thalamo-cortical system may be a contributory factor in the lack of DLB reactivity.

In contrast to the DLB group, the AD group reactivity was broadly comparable to that of the controls. However, the AD group did exhibit some atypical reactivity following cue presentation which tended to be region-specific; deficits were most evident over the left parietal region (across a broad frequency range). Relative to the cue conditions, the AD group exhibited a lack of oscillatory reactivity across a greater number of regions following the presentation of a target, particularly the incongruent target (with a lack of theta ERS across the majority of regions). These findings indicate that the aberrant reactivity in the AD group was primarily associated with processing stimuli necessitating higher order cognitive functioning (where there is an element of executive functioning involved), which is in alignment with the extensive literature documenting executive impairments in AD patients (Baudic et al., 2006; McGuinness et al., 2010).

Attentional network oscillatory reactivity

For the alerting network, the DLB group showed a profound lack of oscillatory reactivity which was most apparent in the lower frequencies of interest (< 30 Hz). In particular, DLB patients exhibited diminished global theta ERS (evident across the majority of the 500 ms interval); this ERS was attenuated relative to both the AD and control groups, and thus was characteristic of the DLB group. In contrast, the AD group reactivity associated with the alerting effect was broadly comparable to that of the controls. These findings are

indicative of different aetiological mechanisms underlying the reduced alerting efficiency which was evident in both dementia groups from a behavioural perspective. Given that the alerting network is modulated by noradrenergic projections from the locus coeruleus (Coull et al., 2001; Raz, 2004), and a scarcity of locus coeruleus noradrenergic neurons has been observed in DLB patients (Szot et al., 2006), reduced integrity of the locus-coeruleus noradrenergic system may be contributing to the diminished low frequency neuronal reactivity associated with the reduced ability to maintain an alert state in DLB patients.

In the DLB group, a lack of theta ERS associated with the alerting network, evident between 200-450 ms over the right parietal region, was associated with greater severity of clinically assessed cognitive fluctuations. The parietal regions are known to be markedly affected in DLB (Colloby et al., 2002), in particular the right parietal lobe (Blanc et al., 2015; Delli Pizzi et al., 2014a). Attenuated theta ERS over the right parietal region may therefore be an important factor underlying the pathophysiology of cognitive fluctuations in DLB.

With regard to the orienting and executive conflict effects, the oscillatory reactivity was broadly comparable across all groups; primarily intermittent ERS and ERD, of reduced power relative to the alerting network, diffuse across the time and frequency domains in all regions. Although the dementia groups exhibited reduced executive conflict processing behaviourally, the time-frequency analyses showed that whilst there were group x time interactions in the gamma range for the executive conflict effect, when investigated further the ERSP differences between the groups in this frequency range were minimal. These findings are consistent with the Firbank et al. (2015) study which demonstrated reduced behavioural executive conflict efficiency in the dementia groups, yet comparable fronto-parietal and lateral occipital executive conflict activations across all groups (AD, LBD, controls). The authors suggested that this indicates that the dementia groups employed the same distributed executive network as the controls, as opposed to having region-specific deficits.

9.2 Conclusions

To summarise, this study has characterised the oscillatory reactivity associated with the attentional networks using a modified version of the ANT suitable for use in dementia cohorts. Furthermore, this study has established how attentional network efficiency is

differentially affected in LBD patients relative to AD patients and age-matched controls, and has identified aberrant oscillatory reactivity associated with dysfunction of the attentional networks in DLB patients. The profound lack of global oscillatory reactivity exhibited by the DLB patients in response to the presentation of the task stimuli, postulated to be due to reduced integrity of the cortico-thalamic system, fits with the notion that global (as opposed to region-specific) network dysfunction may contribute to the cognitive phenotype of LBD (Firbank et al., 2015; Peraza et al., 2015; Taylor et al., 2013). With regard to the attentional networks, attenuated low frequency global reactivity in the DLB group, specific to the alerting network, is indicative of this fractionated aspect of attention (the ability to maintain an alert state) being differentially affected in DLB patients relative to AD patients and controls. Furthermore, there is evidence to suggest that attenuated theta ERS over the parietal lobe may contribute to the underlying pathophysiology of cognitive fluctuations in DLB.

9.3 Strengths and limitations

CATFieLD study

The study was based on a large cohort of patients, who underwent rigorous neuropsychiatric and neuropsychological assessment (across numerous cognitive domains) as well as physical assessment to ensure that they were suitable to participate in the study. This extensive assessment procedure ensured that the patients were well classified with respect to cognitive functioning and dementia diagnosis (as far as possible).

An inevitable confound of clinical research of this nature is there is a selection bias concerning those individuals consenting to participate. This is particularly true of the healthy controls who volunteer; it is probable that such individuals are high functioning and may not be representative of the general population. Furthermore, to ensure that the participants were able to understand and complete the task, a MMSE score of above 12 was a participatory requirement for the dementia patients, and indeed the average MMSE score of patients with dementia who participated was relatively high (AD: 21.74, SD: 3.23; LBD: 22.19, SD: 3.47). Consequently, the inferences drawn from the attentional network analyses may not be able to be extrapolated to individuals with more severe dementia. It is possible that had more impaired patients been recruited, greater differences would have been evident between the

dementia patients and elderly controls with regard to attentional network efficiency. However, it was not feasible to conduct a study of the attentional networks using a severely impaired patient cohort who were unable to comprehend the ANT, and it is notable from the EEG perspective that marked differences in oscillatory reactivity were evident even in patients with mild dementia.

The vast majority of the patients in the study were taking psychotropic medication, including cholinesterase and dopaminergic medication. This potential medication confound is highly salient as it is postulated that the orienting and executive conflict networks are modulated by the basal forebrain cholinergic system and dopaminergic system respectively (Fan et al., 2005). Furthermore, cholinesterase inhibitors have been found to enhance attentional function in dementia cohorts (Emre et al., 2004; McKeith et al., 2000a). This limitation is fully acknowledged however it would be have been unethical to request that participants cease to take medication for the purposes of this study. However, as discussed in chapters 3 and 5, when medication usage was covaried for in the analyses, there were no significant medication effects or interactions.

Modified ANT paradigm

Our modified ANT was designed to create a version of the task suitable for assessing attentional network efficiency in dementia cohorts using electrophysiological and neuroimaging approaches. Despite various alterations to the design of the task relative to the original ANT (discussed in chapter 2), as described in chapter 8 in our elderly control participants the modified ANT elicited oscillatory reactivity comparable to that previously reported in an ANT study of an elderly cohort (Deiber et al., 2013). Furthermore, the vast majority of the participants were able to complete the task, suggesting that the modified ANT is suitable for probing attentional function in elderly cohorts and individuals with dementia of mild to moderate severity.

Analyses methods

As discussed throughout this thesis, the behavioural analyses (chapter 3) were conducted using an LBD group comprising DLB and PDD patients, whereas for the EEG analyses a

subsample of this group was used, comprising DLB patients only. A greater severity of aberrant motor activity was noted in the PDD patients relative to the DLB patients, and thus the PDD patients' EEG data tended to contain substantial movement artefacts. To remove such artefacts would require extensive pre-processing of the data (more so than the DLB patients) and it was therefore decided that the DLB and PDD patients should be treated as separate groups for the EEG analyses. For the purposes of this thesis, only the DLB patients' data was analysed due to the extensive and time-consuming nature of the analyses conducted. However, in the future it would be of interest, and important, to compare the attentional network reactivity of the DLB and PDD patients.

9.4 Future directions

Whilst is it is postulated that the profound lack of reactivity exhibited by the DLB group may be due to reduced integrity of the thalamo-cortical system (see section 9.1.2), the time-frequency analyses were conducted using regions defined according to location over the scalp, and thus from these analyses it is not possible to deduce the extent to which various structures, particularly subcortical structures such as the thalamus, contributed to this aberrant reactivity. In order to investigate this it would be useful to conduct a source localisation analysis of the ANT data. Indeed this has been done previously, with Fan et al. (2007) conducting a source localisation analysis of ANT data using dipole modelling, where the dipole locations were constrained using activation clusters from an earlier fMRI study of the ANT (Fan, 2005). As the CATFieLD study participants also underwent fMRI whilst performing the ANT (during a separate recording session), it is feasible that a comparable source localisation analysis could be conducted. Nevertheless, modelling subcortical structures such as the thalamus will be challenging when using EEG which is most sensitive to electrical activity within the cortical mantle (Kirschstein & Kohling, 2009).

The time-frequency analyses were conducted using the mean ERSP across all of the task trials (for each participant), consequently from these results it is not possible to make inferences regarding the variability in the oscillatory reactivity across trials (within-subject ERSP variability). A measure of trial by trial variability may be more likely to correlate with clinically assessed cognitive fluctuations, as it would be an indicator of attentional variation over the duration of the task. One such measure of trial by trial variability is inter-trial

coherence (ITC): a measure of event-related phase coherence (phase locking) across trials (Delorme & Makeig, 2004) . Output values generated during ITC estimation are a number between 0 and 1; a higher value denotes greater phase coherence across trials at a given frequency and latency, i.e. greater synchronisation (phase locking) between the activity and the time-locking event. Given that mind wandering in healthy individuals has been found to be associated with reduced theta phase coherence (trial to trial consistency in response to perceptual events) peaking over parietal regions (Baird et al., 2014), it would be of interest to investigate if the DLB patients exhibited reduced theta phase coherence. Although not discussed in this thesis, using the time-frequency parameters (described in chapter 5) ITC values were calculated for each participant (for each cue and target condition) for potential future analyses.

The results of the time-frequency analyses were derived from separate analyses for each task condition (cue and target, and attentional networks). From the target data, it was therefore not possible to deduce the extent to which the post-cue oscillatory activity (prior to the target onset) affected the target activity, or the interactions between the networks. Given that previous ANT studies have shown interactions between the attentional networks, in particular a modulatory effect of alerting on orienting and executive conflict effects (Fernandez-Duque & Black, 2006; Fuentes et al., 2010), it would be of interest to investigate how the post-cue reactivity affects the post-target reactivity, particularly as Fuentes et al. (2010) found that an alerting cue had a greater modulatory effect on the orienting and executive conflict networks in DLB patients relative to AD patients. Furthermore, in the CATFieLD participant cohort, Firbank et al. (2015) observed parietal target activations which were greater following cues than the no cue condition in LBD patients, however this was not evident in the AD and control groups. It would therefore be of interest to investigate this cue-target interaction in the CATFieLD LBD group from an EEG time-frequency perspective.

With regard to the ERSP correlation analyses there is plenty of scope for further exploratory analyses. The correlation analyses for the clinical fluctuation measures (presented in chapter 7) focused only on the attentional network effects; in the dementia groups only the activity which was significantly different to the control group was investigated. This was a strategic attempt to identify aberrant reactivity pertaining to the attentional networks which was most likely to be associated with clinically assessed cognitive fluctuations in DLB. However, given that group differences were more evident in the absolute ERSP associated

with the cue and target conditions (as opposed to the attentional network effect ERSP), it would be of interest to investigate if the cue and target reactivity is associated with the key clinical fluctuation variables. Furthermore, it would be of interest to conduct a between-group analysis of the ERSP time-locked to the participants' responses following target presentation, and investigate how this oscillatory reactivity relates to the RT and clinical fluctuation measures.

Finally, it would be of interest to examine the EEG data from an ERP perspective. As discussed in chapter 1, the ERP literature pertaining to the ANT is limited, however there is some evidence to suggest that the ANT stimuli elicit certain components in healthy individuals, particularly N100 and P300. Given the atypical nature of the P300 component that has been observed in DLB patients, in particular delayed latency which has been found to correlate with cognitive fluctuation severity (Bonanni et al., 2010), it would be of interest to investigate the P300 component in DLB patients in the context of the attentional networks. Furthermore, in an ANT study of healthy individuals Neuhaus et al. (2010) found the alerting effect to be associated with increased N100 amplitude over the parietal cortex; the authors suggested this was indicative of this network engaging selective attentional processes during the early stages of visual processing. Given that alerting parietal theta ERS in our DLB group was associated with cognitive fluctuation severity, and that theta activity has been found to be a contributory factor in the manifestation of the N100 component (Makeig et al., 2002), it would be of interest to conduct N100 ERP analyses (post-cue, post-target and attentional networks). Preliminary post-cue ERP data for the parietal regions is presented in appendix B; from this there are apparent group differences in the time ranges corresponding to the N100 and P300 components. It would therefore be of interest to conduct statistical analyses of this data in order to determine whether this, in conjunction with the ERSP data, may be useful for characterising the neurophysiology underlying attentional dysfunction in DLB.

Appendix A. Publications relevant to this thesis

Cromarty, R. A., Elder, G. J., Graziadio, S., Baker, M., Bonanni, L., Onofrj, M., O'Brien, J. T., & Taylor, J-P. (2016). Neurophysiological biomarkers for Lewy body dementias. *Clinical Neurophysiology*, *127*(1), 349-359.

Please note adapted sections of chapter 1 (section 1.4) have been included in the above review article.

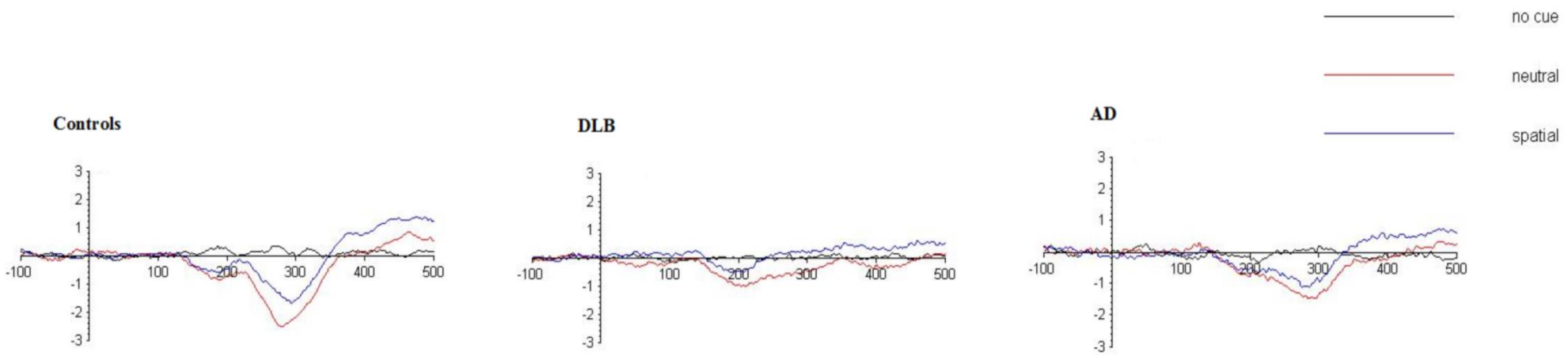
Cromarty, R., Graziadio, S., Colloby, S., Killen, A., Peraza, L.R., Elder, G., Firbank, M., Thomas, A., McKeith, I., O'Brien, J., & Taylor, J-P. (2015). Electrophysiological correlates of attentional dysfunction in dementia with Lewy bodies. *In: International Dementia with Lewy Bodies Conference 2015*. Ft. Lauderdale, FL, USA: American Journal of Neurodegenerative Disease.

Johnsen, K., Cromarty, R., Jóhannesson, G. H., Johannsson, M., & Taylor, JP. (2014). Validation of the sigla indicies in an independent cohort: A new way forward for the differential diagnosis of dementias? *Alzheimer's and Dementia*, *10*(4), 350-351.

Colloby, S. J., Cromarty, R. A., Peraza, L. R., Johnsen, K., Jóhannesson, G., Bonanni, L., Onofrj, M., Barber, R., O'Brien, J. T., & Taylor, J-P. (2016). Multimodal EEG-MRI in the differential diagnosis of Alzheimer's disease and dementia with Lewy bodies. *Journal of Psychiatric Research, 78*, 48-55.

Appendix B. Preliminary ERP data

Parietal region cue ERPs



Grand average ERPs (event-related potentials) elicited by the presentation of cues (no cue, neutral cue, spatial cue) during the ANT (Attention Network Test) for the controls, DLB and AD groups. The x axis represents time (ms) from cue onset (0 ms represents cue presentation), the y axis represents the amplitude (μV) of the signals. The ERPs were calculated by averaging the signal of electrodes located over the parietal regions.

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