EEG Coherence and Executive Function in Mild Cognitive Impairment and Alzheimer's Disease: An Examination of Resting Coherence and Coherence During Executive Functioning Tasks

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ABSTRACT

EEG Coherence and Executive Function in Mild Cognitive Impairment and Alzheimer's Disease: An Examination of Resting Coherence and Coherence During Executive Functioning Tasks

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Deficits in executive functioning have been reported in the early stages of Alzheimer's disease (AD) and in mild cognitive impairment (MCI); however, the neural underpinnings of these deficits remain unclear. It has been proposed that AD can be characterized as a disconnection syndrome, where functional connectivity between brain regions is compromised. Therefore, it may be hypothesized that altered functional connectivity may be related to executive functioning in MCI and AD. The research presented in this dissertation examined group differences for MCI and AD patients relative to controls for EEG coherence within a fronto-parietal network measured at rest (Study 1), during a Go/No-go inhibitory control task (Study 2), and during an N-back working memory task (Study 3). The relationships between coherence and measures of cognition and brain integrity (cortical thickness and PiB retention) were also explored.

Results indicated that AD patients, but not MCI patients, had reduced resting coherence between cross-hemisphere parietal regions versus normal controls, and that MCI patients who later converted to dementia had higher resting fronto-parietal coherence versus MCI patients who remained stable. Furthermore, both AD and MCI patients showed altered coherence during task performance. During both tasks, AD patients showed reduced coherence and less of a task-related increase in coherence versus controls (for cross-hemisphere electrode pairs during the Go/No-go task and for cross-hemisphere and fronto-parietal pairs during the N-back task). In contrast, in comparison to controls, MCI patients had higher fronto-parietal coherence during the Go/No-go task and a larger task-related increase in fronto-parietal coherence for both tasks, but less of a task-related increase in cross-hemisphere frontal coherence for both tasks. Correlational analyses showed different relationships between EEG coherence and cognition and brain

integrity across groups, with some evidence of a potential compensatory mechanism for higher coherence in controls and MCI patients in some conditions.

These results demonstrate that functional connectivity within a fronto-parietal network is altered in AD patients and MCI patients during the performance of executive tasks. In AD patients, coherence is decreased, whereas MCI patients show a potential compensatory increase in fronto-parietal coherence. The implications of these findings and directions for future research are discussed.

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CONTRIBUTIONS OF AUTHORS

All three studies included in this thesis were conceptualized by Erin Johns, with guidance from Natalie Phillips. For the EEG data, Erin Johns created the stimuli, recruited the participants, designed and conducted the experiments, and processed and analyzed the data under the supervision of Natalie Phillips. Other members of the Cognition, Aging, and Psychophysiology Laboratory contributed to participant recruitment and testing. For Study 1, Howard Chertkow oversaw recruitment, diagnosis, diagnostic and neuropsychological workup, characterization, and progression of patients included in the study; James Nikelski carried out data processing and analysis for PiB and cortical thickness measurements; and Jean-Paul Soucy organized, instantiated, and oversaw the PiB-PET scanning technical details, and provided reads on the PET pattern result. All results were interpreted collaboratively by Erin Johns and Natalie Phillips. Erin Johns wrote the first draft of the manuscripts, with a subsequent revision by Natalie Phillips.

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LIST OF ABBREVIATIONS

Aβ……Amyloid-β
AD……...Alzheimer' disease
AUC……Area under the curve
BOLD……...Blood-oxygen-level-dependent
CR……Cognitive reserve
CRUNCH……Compensation-related utilization of neural circuits hypothesis
CVLT……..California Verbal Learning Test
DLPFC……Dorsolateral prefrontal cortex
DMN……..Default mode network
EEG……Electroencephalography
EOG……Electro-oculogram
FDG……2-[18F]fluoro-2-deoxy-D-glucose
FFT……Fast Fourier transform
fMRI……...Functional magnetic resonance imaging
GDS……..Geriatric depression scale
HAROLD……...Hemispheric asymmetric reduction in older adults
LNS……..Letter-number sequencing
MCI……Mild cognitive impairment
MEG……Magnetoencephalography
MMSE……...Mini-mental state examination
MNI……Montreal Neurological Institute
MoCA……Montreal Cognitive Assessment
NEC……Normal elderly controls
NFT……...Neurofibrillary tangles
PET……Positron emission tomography
PiB……Pittsburg Compound-B
ROI……Region of interest
rs-fMRI……..Resting state functional magnetic resonance imaging
RT……Reaction time
SAS……..Supervisory attention system

SMCS……Subjective Memory Complaints Scale
SPECT……...Single photon emission computerized tomography
TMS……Transcranial magnetic stimulation
VLPFC……..Ventrolateral prefrontal cortex
WAIS-III……...Wechsler Adult Intelligence Scale Third Edition
WM……Working memory

CHAPTER 1: GENERAL INTRODUCTION

There is no question that dementia is one of the most significant health concerns in Canada and worldwide. A recent study by the Alzheimer Society of Canada reported that there are currently 747,000 Canadians living with some form of cognitive impairment, and that this number is expected to double to 1.4 million by 2031 (Alzheimer Society of Canada, 2012). Worldwide, the estimated prevalence of dementia was 35.6 million in 2010, with 7.7 million new cases each year (World Health Organization, 2012). But, the impact of dementia extends far beyond these numbers – in Canada in 2011, family caregivers spent 444 million unpaid hours caring for someone with dementia (Alzheimer Society of Canada, 2012), a role that is associated with significant adverse psychological and physical impacts (World Health Organization, 2012). The most common form of dementia is Alzheimer's disease (AD), which accounts for approximately 64% of all dementias in Canada (Canadian Study of Health and Aging Working Group, 1994). With so many people impacted by AD, research into all aspects of the disease continues to be of utmost importance.

Though our knowledge of the neuropathology of AD has advanced greatly over the past 100 years, there are still many unanswered questions and gaps in our understanding of the disease. In particular, there is still much to learn about how the disease impacts brain functioning and the relationship between brain functioning and cognitive functioning.

Though the most common and prominent feature of early AD is a deficit in episodic memory (Albert, 2008; Collie & Maruff, 2000; Peña-Casanova, Sánchez-Benavides, de Sola, Manero-Borrás, & Casals-Coll, 2012; Weintraub, Wicklund, & Salmon, 2012), several other cognitive domains, including deficits in semantic memory, language, and executive functioning, have been reported to be affected in early (Albert, 2008; D. P. Salmon & Bondi, 2009; Silverberg et al., 2011; Weintraub et al., 2012) and even prodromal AD (Albert, 2008; Collie & Maruff, 2000; D. P. Salmon & Bondi, 2009; Yanhong, Chandra, & Venkatesh, 2013). While episodic memory deficits clearly map on to the neuropathology of AD (specifically neurofibrillary tangles, synaptic dysfunction, and neuronal loss in the medial temporal lobes; Albert, 2008; Peña-Casanova et al., 2012; Weintraub et al., 2012), the neurological underpinnings of other cognitive deficits are less clear. For example, atrophy of the frontal lobes is not typically seen in the early phases of AD (Whitwell, Przybelski, et al., 2007b), therefore it is likely that other neuropathological processes contribute the executive dysfunction that has been reported in the

early phases of the disease. It has been posited by several researchers (e.g., Bokde, Ewers, & Hampel, 2009; De Lacoste & White, 1993; Delbeuck, Van der Linden, & Collette, 2003) that AD may be thought of as a syndrome of disconnection between brain areas. As executive functions depend on the coordination of multiple brain regions (Elliott, 2003; Royall et al., 2002), this functional disconnection between brain regions could explain executive dysfunction in early and preclinical AD.

This dissertation contributes to our understanding of functional connectivity in AD by examining electroencephalogram (EEG) coherence in AD and amnestic mild cognitive impairment (MCI). MCI is a term to describe individuals who exhibit some early signs of AD (e.g., objective impairments in episodic memory functioning), but do not meet the criteria for AD. Often, MCI represents a transitional stage between normal aging and AD (Petersen et al., 2014). This dissertation comprises three manuscripts. The first paper examines spontaneous EEG coherence (i.e., EEG recorded while at rest) in MCI and AD and its relationship with certain measures of AD neuropathology (cortical thickness and amyloid deposition) and neuropsychological test performance. The following two papers examine the relationship between EEG coherence and executive functioning by (1) measuring EEG coherence during the performance of executive functioning tasks, and (2) examining the relationships between coherence and cognitive performance and between coherence and neuropathological measures. The first of these two papers investigates a measure of inhibitory control (Go/No-go task) and the second paper examines a measure of working memory (N-back task).

The introductory section of this dissertation includes a review of the issues at hand, and is broken down into three main sections:

(1) A description of AD and MCI, including the neuropathology of these disorders and the relationship between neuropathology and cognition;

(2) A description of executive functions, with a particular focus on inhibitory control and working memory and a review of the current literature on executive functioning in AD and MCI;

(3) A description of EEG coherence and review of the literature on EEG coherence and executive functioning and EEG coherence in AD and MCI.

1.1. Alzheimer's Disease

Alzheimer's disease is a progressive neurodegenerative disorder characterized by

multiple cognitive deficits and complex neuropathological changes. A definite diagnosis of AD can only be made after post-mortem histopathological confirmation is obtained; therefore, the term probable AD is used for in vivo diagnosis. The most commonly used diagnostic criteria are the National Institute of Neurological and Communicative Disorders and Stroke – Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria, which include progressive cognitive impairment in two or more cognitive domains (confirmed by clinical examination and neuropsychological testing), interference with functional abilities, and the absence of other diseases which could produce the dementia syndrome (McKhann et al., 1984). Recently, these diagnostic criteria have expanded somewhat to include a gradual, insidious onset and the specification of a predominantly amnestic or nonamnestic presentation as well as the inclusion of increased levels of certainty of diagnosis with evidence for the presence of genetic or pathophysiological markers (McKhann et al., 2011). As previously mentioned, the typical clinical presentation involves prominent episodic memory impairment; however, impairment in at least one other cognitive domain, including executive functioning, visuospatial abilities, language functions, or personality/behaviour changes must be present for a diagnosis of probable AD to be made.

The gross neuropathology of AD involves cerebral atrophy affecting both gray matter and white matter that varies widely in severity and distribution. In some cases, the temporal lobes, hippocampus, and amygdala are selectively affected by atrophy, and severe, generalized atrophy is more characteristic of early onset AD (Esiri, 2001). The narrowing of gyri and widening of sulci may also be present, and the lateral and third ventricles may be enlarged (Esiri, 2001).

Two of the pathological hallmarks of AD are amyloid-β (Aβ) plaques and neurofibrillary tangles (NFTs). Amyloid plaques are extracellular aggregations consisting of mainly Aβ peptides (particularly Aβ40 and Aβ42), but also other proteins, growth factors and their receptors, and many other molecules (Esiri, 2001; Lage, 2006; Nelson, Braak, & Markesbery, 2009; Perl, 2010). With the recent development of amyloid imaging techniques using positron emission tomography (PET), it has become possible to examine the pattern of amyloid deposition in vivo. The most well-known radiotracer used in this technique Pittsburgh Compound-B (PiB), which binds to cortical areas containing amyloid deposits (Klunk et al., 2004). PiB retention has been found to be elevated in AD patients in comparison to normal controls, particularly in the middle frontal and prefrontal cortex, parietotemporal cortex, posterior cingulate cortex, precuneus,

occipital lobes, thalamus, and striatum (Berti et al., 2010; Masdeu, Kreisl, & Berman, 2012). NFTs are abnormal filaments of hyperphosphorylated tau contained inside cell bodies, and they are most prominently found in the entorhinal cortex, the CA1 and subicular region of the hippocampus, the amygdala, and the deeper layers of the neocortex (Esiri, 2001; Perl, 2010). Amyloid plaques are not associated with neurodegeneration in the absence of NFTs or amyloid angiopathy, thus it has been argued that NFTs are more likely to be the cause of neurodegeneration (Nelson et al., 2009).

There are several other neuropathological features of AD, including neuronal cell loss (particularly in the CA1 region of the hippocampus, the basal nucleus, the dorsal raphe nucleus, and the locus coeruleus), synaptic loss, white matter loss, glial cell reactions (e.g., enlarged astrocytes, increased microglial cells), neuropil threads, and amyloid angiopathy (Esiri, 2001; Perl, 2010; Thompson et al., 2007). Structural changes have been reported in several white matter tracts including the cingulum bundle, uncinate fasciculus, corpus callosum, anterior commissure, and superior longitudinal fasciculus (Matthews, Filippini, & Douaud, 2013). In addition, neurochemical changes are also present, including a lack of cholinacetyltransferase and the loss of cholinergic neurons, as well as increased glutamate, which produces excitotoxicity and cell death (DeKosky, 2001; Lage, 2006).

Metabolic activity, measured with 2-[18F]fluoro-2-deoxy-D-glucose (FDG) PET and single photon emission computerized tomography (SPECT) have been used as an index of synaptic functioning and density (Berti et al., 2010; Román & Pascual, 2012). AD patients show reduced glucose metabolism and decreased blood flow in the medial temporal lobes, the parietotemporal cortex, and the posterior cingulate cortex, and also in the frontal cortex in the later stages of the disease. This is in addition to a widespread global metabolic impairment (Berti et al., 2010; Masdeu et al., 2012; Román & Pascual, 2012).

Post mortem autopsy studies (e.g., Arnold, Hyman, Flory, Damasio, & Van Hoesen, 1991; H. Braak & Braak, 1991; 1997; J. L. Price, Davis, Morris, & White, 1991) and neuroimaging studies (e.g., Thompson et al., 2007) have found that AD pathology progresses in a predictable pattern. Low-density amyloid deposition is initially seen in basal portions of frontal, temporal, and occipital lobes, followed by moderate densities in the cortical association areas and mild deposition in the hippocampus. In the final stages of the disease, amyloid deposits are densely packed in all cortical areas (including primary cortical areas) and deposits

are also seen in subcortical areas such as striatum, thalamus, hypothalamus, and subthalamic nucleus. In contrast, NFT pathology begins in the entorhinal cortex and the CA1 region of the hippocampus, followed by the amygdala, basolateral nuclei, claustrum, basal putamen, and nucleus accumbens. The final stages of the illness are characterized by widespread pathology in the hippocampus and the association cortices (Arnold et al., 1991; H. Braak & Braak, 1991; J. L. Price et al., 1991). Cerebral atrophy progresses in a similar pattern to that of NFTs (Whitwell, Przybelski, et al., 2007b). Cortical thinning is evident in the entorhinal cortex in the early phases of the illness (Román & Pascual, 2012) and in the late stages, many brain areas are affected by cortical thinning including most prominently the medial temporal lobes, but also the anterior and posterior cingulate region, frontal lobes, inferior parietal lobes, orbitofrontal cortex, and visual association cortex (Lerch et al., 2005). Cortical areas that myelinate first and most heavily, such as primary sensory cortices, tend to be the most resistant to AD pathology (H. Braak, Rüb, Schultz, & Tredici, 2006; Mesulam, 2000).

1.1.1 Functional brain connectivity. Given evidence that synaptic dysfunction is present very early in the course of the disease, and possibly years before the onset of clinical symptoms, researchers have begun to focus on functional neuroimaging to detect alterations in brain functioning. It is hypothesized that AD is a syndrome of disconnection between brain areas and that a focal lesion may disrupt network functioning, thus affecting a wider range of brain areas and cognitive functions. Thus, the neuropathology of AD may result in the disruption of functional connectivity and the failure of the brain to integrate various regions into effective networks, and this may underlie changes in cognitive functioning (Bokde et al., 2009; Delbeuck et al., 2003; D. P. Salmon & Bondi, 2009). The fact that the neuropathology of AD spreads through large cortico-cortical pyramidal neurons is taken as evidence for the disconnection hypothesis of AD (Bokde et al., 2009; Delbeuck et al., 2003).

Resting-state functional magnetic resonance imaging (fMRI) has been used to evaluate fluctuations in blood-oxygen-level-dependent (BOLD) signal and correlations between these fluctuations in spatially distant brain regions (Gomez-Ramirez & Wu, 2014; Sheline & Raichle, 2013). Several resting state functional networks have been identified using this technique, of which the most extensively studied is the default mode network (DMN). The DMN represents a collection of brain areas that are particularly active during rest and become "deactivated" during the performance of a cognitive task. The brain regions involved include the medial prefrontal

cortex, anterior cingulate cortex, posterior cingulate cortex, precuneus, parietal cortex, and hippocampus, as well as some regions of the cerebellum, thalamus, and temporal lobes (Beason-Held, 2011; Hafkemeijer, van der Grond, & Rombouts, 2012; Matthews et al., 2013; Sheline & Raichle, 2013). These same brain regions vulnerable to various aspects of the neuropathology of AD including atrophy, amyloid deposition, and hypometabolism (Beason-Held, 2011; Hafkemeijer et al., 2012; Matthews et al., 2013; Silverberg et al., 2011; Weintraub et al., 2012). In normal aging, decreased functional connectivity has been observed in the frontal gyrus, posterior cingulate cortex, and parietal cortex, and the network of brain regions involved in the DMN is larger in comparison to younger adults (e.g., inclusion of the inferior and middle frontal cortex; Beason-Held, 2011; Hafkemeijer et al., 2012). In AD patients, decreased DMN functional connectivity has been reported in the medial temporal lobes and posterior cingulate cortex/precuneus in the early stages, extending to include the medial prefrontal cortex, anterior cingulate cortex, and lateral parietal regions in the later stages (Balachandar et al., 2014; Beason-Held, 2011; Bokde et al., 2009; Hafkemeijer et al., 2012; Pievani, de Haan, Wu, Seeley, & Frisoni, 2011; for a more comprehensive review of the literature, see Filippi & Agosta, 2011). However, some studies also reported increased connectivity in the medial prefrontal cortex, posterior cingulate cortex, parietal cortex, and hippocampus, which has been interpreted as evidence for the compensatory-recruitment hypothesis (Filippi & Agosta, 2011; Hafkemeijer et al., 2012). Furthermore, AD patients demonstrate decreased efficiency of deactivation of the DMN during the performance of cognitive tasks in the medial parietal region, posterior cingulate, and anterior cingulate cortex (Bokde et al., 2009; Filippi & Agosta, 2011).

Altered connectivity has also been reported in other functional networks examined with fMRI, including the dorsal attention network, fronto-parietal central executive network, salience network (which includes most prominently the dorsal anterior cingulate and orbital frontoinsula), and sensory motor network (Brier et al., 2012). For example, decreased functional connectivity has been observed in the fronto-parietal network (Agosta et al., 2012; Dhanjal & Wise, 2014; K. Wang et al., 2007; Z. Wang et al., 2013), whereas increased connectivity has been reported in the frontal and salience networks (Agosta et al., 2012; Balachandar et al., 2014; K. Wang et al., 2007; L. Wang et al., 2006; H.-Y. Zhang et al., 2009; J. Zhou et al., 2010; however, see Dhanjal & Wise, 2014 for decreased connectivity in the salience network). Studies of global brain

functional connectivity have reported a general pattern of decreased anterior-posterior connectivity and greater connectivity within lobes (Filippi & Agosta, 2011).

While resting state fMRI studies can provide an index of functional connectivity on a timescale of seconds, EEG and magnetoencephalography (MEG) studies examine synchronous oscillations on a timescale of milliseconds. This synchronization can be quantified using a number of different methodologies, including phase synchronization, coherence, and synchronization likelihood (Pievani et al., 2011). Coherence studies will be reviewed in greater detail below; however, briefly, AD patients have demonstrated decreased connectivity in fronto-parietal and fronto-temporal regions in the alpha and beta frequency bands (Pievani et al., 2011).

1.2 Mild Cognitive Impairment

Since the original characterization of mild cognitive impairment as a diagnostic entity (Petersen et al., 1999), this topic has been the subject of intense research interest (Petersen et al., 2009). Individuals with MCI convert to dementia at a rate of approximately 5-10% per year in contrast to 1-2% in healthy controls (Petersen, 2011), and it has been argued that, in many cases, MCI may represent a prodromal stage of AD or other forms of dementia (Petersen et al., 2014). As such, MCI represents an important group for the early identification of those at risk of developing dementia, as well as for implementing early treatment options.

While the original conceptualization of MCI focused specifically on memory impairment, the concept has broadened to now encompass a variety of clinical profiles and underlying causes. The revised National Institute on Aging-Alzheimer's Association (NIA-AA) diagnostic criteria (Albert et al., 2011) include a reported cognitive complaint (self or informant), objective cognitive impairment, preserved functional abilities, and failure to meet diagnostic criteria for dementia. This broad definition can then be broken down into two main subtypes of MCI: (1) amnestic MCI (aMCI), defined by the presence of episodic memory impairment, and (2) nonamnestic MCI (naMCI), defined by impairment in one or more non-memory cognitive domains. The impairment can further be classified as single domain (impairment restricted on one cognitive domain), or multiple domain (impairment in two or more cognitive domains). Thus, there are four possible subtypes of MCI: (1) single domain aMCI, (2) multiple domain aMCI, (3) single domain naMCI, and (4) multiple domain naMCI. These subtypes may represent the prodromes of different types of dementia. For example, 70-90% of aMCI patients who progress to dementia exhibit clinical signs of AD (Petersen et al., 2009; 2001), and naMCI

patients may progress to non-AD dementing conditions such as frontotemporal dementia, Lewy body dementia, or vascular dementia (Jak et al., 2009; Petersen et al., 2009). The current consensus is that most MCI patients who go on to develop AD most commonly exhibit an impairment in episodic memory, though other cognitive domains may also be impaired (Albert et al., 2011). As the focus of this dissertation is on AD and MCI due to AD, the remainder of this literature review will focus on aMCI. Earlier research studies did not commonly specify the subtype of MCI examined; however, where not specified, MCI patients are typically defined by the presence of an episodic memory impairment, thus would fall into the category of aMCI (single or multiple domain).

The neuropathological features of aMCI are typically intermediate between normal aging and very early AD, including the presence of neurofibrillary tangles in the medial temporal lobes, diffuse cortical amyloid deposition, synaptic loss, and degeneration of the cholinergic system (Drago et al., 2011; Mufson et al., 2012; Petersen et al., 2006; Stephan et al., 2012). However, there is considerable heterogeneity in the presence of the gross neuropathological features of the AD, with many MCI patients not showing significant neuropathological changes (Mufson et al., 2012; Stephan et al., 2012). Nevertheless, significant neuronal loss in the entorhinal cortex and hippocampus has been reported in MCI (Mufson et al., 2012; Stephan et al., 2012). Neuroimaging studies have reported atrophy of the medial and inferior temporal lobes in both single and multiple domain aMCI, as well as atrophy of the posterior temporal lobe, parietal association cortex, and posterior cingulate cortex in multiple domain aMCI (Whitwell, Petersen, et al., 2007a). MCI patients also demonstrate reduced cortical thickness in the temporal cortex and precuneus (Román & Pascual, 2012). In comparison to MCI patients who remain stable over 7 years, MCI patients who convert to AD show greater cortical thinning at baseline in the superior and middle frontal gyri, superior, middle, and inferior temporal gyri, the fusiform gyrus, and parahippocampal regions (Julkunen et al., 2009).

Hypometabolism has been reported in the medial temporal lobes, parietotemporal cortex, and posterior cingulate cortex in aMCI, and metabolic impairment in these regions is predictive of conversion to AD (Berti et al., 2010; Petersen et al., 2014). PiB retention with a similar distribution as seen in AD has been reported in approximately 50% of amnestic MCI patients, and PiB retention has been reported in up to 22% of normal elderly controls (Berti et al., 2010). In MCI patients, those who convert to AD have greater baseline PiB uptake than those who do

not convert (Berti et al., 2010). However, only about one half of MCI patients who are considered to be PiB positive also demonstrate reductions in glucose metabolism, and diagnostic accuracy raises from 75% to 90% when PiB- and FDG-PET are used together in comparison to PiB-PET alone (Berti et al., 2010). Thus, the presence of amyloid deposition alone does not appear to be sufficient in distinguishing MCI patients from normal controls.

1.2.1 Functional brain connectivity. MCI patients also demonstrate decreased functional connectivity in the DMN, though to a lesser degree than seen in AD. Disconnection is seen particularly in the posterior cingulate cortex, medial prefrontal cortex, anterior cingulate cortex, and hippocampus, and MCI converters show greater disconnection than non-converters (Beason-Held, 2011; Filippi & Agosta, 2011; Hafkemeijer et al., 2012; Pievani et al., 2011; Sheline & Raichle, 2013; Teipel et al., 2013). Decreased deactivation of medial frontal regions during the performance of a cognitive task, which is intermediate between healthy older adults and AD patients, has also been reported (Bokde et al., 2009; Filippi & Agosta, 2011).

The findings regarding the connectivity of other functional networks in MCI have been somewhat mixed. While several studies have reported increased frontal connectivity, similar to what has been observed in AD (Bai et al., 2009; Liang, Wang, Yang, Jia, & Li, 2011; Z. Qi et al., 2010), other studies have reported reduced frontal connectivity (Sorg et al., 2007) or no difference between MCI patients and healthy controls (Agosta et al., 2012). These discrepancies may be due to the heterogeneous nature of MCI. There has been limited research on the fronto-parietal central executive network and salience network in MCI patients; however, two studies have reported no difference between MCI patients and controls in salience network connectivity (Agosta et al., 2012; He et al., 2014), and one study reported no difference in fronto-parietal connectivity (Agosta et al., 2012).

1.3 Neuropathology and Cognition

The relationship between neuropathology and cognition in MCI and AD is complex and not yet fully understood. Generally speaking, the extent and distribution of neurofibrillary tangles have been found to be correlated with disease severity and cognitive impairment, whereas amyloid deposits have not (Arriagada, Growdon, Hedley-Whyte, & Hyman, 1992; Bierer et al., 1995; Giannakopoulos et al., 2009; Powell et al., 2006; Yoshiyama, Lee, & Trojanowski, 2013). However, some recent in vivo amyloid imaging studies have found that PiB uptake is correlated with clinical measures of dementia severity and cognition, whereas other

studies have found no relationship (see Wahlster, Niederländer, Kriza, Schaller, & Kolominsky-Rabas, 2013 for a review). There is some evidence that levels of amyloid deposition may be related to cognitive function in healthy older adults without cognitive impairment and in patients MCI, but not in AD patients (Villemagne et al., 2008), which may be related to the rapid accumulation of amyloid in the early and preclinical phases of the disease followed by a plateau in the later stages (Masdeu et al., 2012). In addition, certain amyloid plaque subtypes and Aβ oligomers have been reported to be correlated with cognitive function (Stephan et al., 2012) and MCI patients who are classified as PiB positive decline in cognitive abilities faster than those who are classified as PiB negative (Jack, Barrio, & Kepe, 2013; Masdeu et al., 2012). Therefore, the extent to which amyloid deposition is correlated with cognitive impairment remains unclear, but emerging evidence is suggestive of a greater relationship than was previously believed.

Other aspects AD neuropathology have also been found to be correlated with cognitive functioning. For example, synaptic loss and atrophy of the entorhinal cortex and hippocampus are associated with performance on the Mini Mental State Examination (MMSE) and neuropsychological measures of episodic memory (Mufson et al., 2012; Stephan et al., 2012; Terry et al., 1991). Cortical thickness of the bilateral parahippocampal gyrus, left superior temporal gyrus, left insula, and left anterior cingulate cortex is associated with MMSE performance (Lerch et al., 2005), and reduced cortical thickness in the temporal lobes and precuneus is also predictive of conversion from MCI to AD (Masdeu et al., 2012). In addition, increasing temporal lobe atrophy in MCI is correlated with progression in cognitive impairment as measured by the MMSE and neuropsychological measures of episodic memory (Drago et al., 2011).

Measures of brain functioning have also been reported to be related to cognitive function. Hypometabolism in the posterior cingulate cortex has been shown to be associated with poorer memory performance and hypometabolism in the middle and superior frontal cortex, posterior cingulate cortex, and precuneus has been shown to be associated with poorer executive functioning (Chao et al., 2009). Effective deactivation of the DMN (specifically in medial parietal areas) is correlated with memory performance (Bokde et al., 2009), and reduced fronto-parietal connectivity has been reported to be related to learning of word lists (Liang et al., 2011). In addition, reduced connectivity between posterior cingulate cortex and temporal cortex is associated with poorer performance on certain cognitive measures in MCI patients (Bai et al.,

2009) and greater frontal connectivity is associated with better performance on tasks of executive functioning (Agosta et al., 2012).

Overall, the current research is indicative of a clear relationship between neuropathology in the medial temporal lobes and episodic memory impairment, but further work is needed to clarify the relationship between neuropathology and other aspects of cognitive impairment. Emerging evidence suggests that a more complete understanding of changes in brain functioning will lead to a greater understanding of the neurological underpinnings of various aspects of cognitive dysfunction in MCI and AD, including deficits in executive functioning, which will be the focus of the remainder of this review.

1.4 Executive Functions

Despite a rich literature on the cognitive construct of executive functions, a precise definition of the term remains elusive (see Goldstein, Naglieri, Princiotta, & Otero, 2014 for a review of numerous definitions of executive functioning). However, it is generally agreed that executive functions represent higher level cognitive control exercised over lower level cognitive functions. Thus, executive functioning involves many different abilities that allow people to plan and execute goal-directed behaviour, meet unanticipated challenges, exert self-control, work with information held in mind, shift focus between multiple tasks, and flexibly modify behaviour as necessary (Diamond, 2013). The cognitive functions subsumed under the term executive functions include response inhibition, divided attention, working memory, planning, judgment, decision-making, and cognitive flexibility (Diamond, 2013; Goldstein et al., 2014; Stuss & Alexander, 2000; Stuss & Levine, 2002). It has been suggested that three core processes, inhibitory control, working memory, and cognitive flexibility, are the building blocks upon which higher order executive functions such as reasoning, problem solving, and planning, are built (Diamond, 2013). Intact executive functioning is essential for normal functioning in everyday life. Individuals with damage to the frontal lobes, which have long been associated with executive functions, typically demonstrate difficulty regulating their behaviour and executing complex tasks (Chung, Weyandt, & Swentosky, 2014).

Several different theories of executive functioning have been proposed over the years, and two of the most influential of these theories are the supervisory attention system model proposed by Norman and Shallice (1986), and the central executive model of working memory proposed by Baddeley and Della Sala (1996). The supervisory attention system model proposes

a two-tier system for the execution of activities. The lower level system, termed *contention scheduling*, is concerned with routine cognitive and motor functions, and the higher-level system, termed the *supervisory attention system* (SAS), modulates contention scheduling in non-routine situations. Therefore, according to this model, routine and automated behaviours, such as brushing one's teeth, are handled by the contention scheduling system. On the other hand, the SAS is responsible for monitoring the activities of the lower level system in order to handle non-routine situations, or situations that are too complex or ambiguous to be handled by contention scheduling. It is proposed that routine situations trigger a source schema that governs the routine behavioural response. However, when confronted with non-routine situations, a temporary new schema must be constructed and implemented in order to cope with the novelty of the situation. Furthermore, the model specifies several distinct processes involved in coping with non-routine situations. These include goal-setting, spontaneous schema generation, episodic memory retrieval of information from related experiences, delayed intention marker realization (in order to implement a plan of action at a later time), implementation of the schema (which includes the use of working memory), monitoring the effectiveness of the schema, and rejection or alteration of the existing temporary schema (for a more complete description of these processes, see Shallice & Burgess, 1996). Thus, the SAS provides a description of intentional control over lower level cognitive processes, or executive functioning, and each of the distinct processes used by the SAS can be thought of as sub-components of executive functioning.

The newer central executive model of working memory (Baddeley & DellaSala, 1996) was influenced by the SAS model. In this model, it is proposed that working memory can be divided into three interrelated components: the central executive, and two subsidiary slave systems, the visuospatial sketchpad and phonological loop. The central executive is responsible for the attentional control of the subsidiary systems, which maintain and manipulate visual and auditory information held in mind. The model was later modified to include the addition of the episodic buffer, which links information across domains to form integrated visual, spatial, and verbal information (Baddeley, 2000). Several processes were proposed to be involved in the central executive, including dual task performance, selective attention, task switching, and accessing and manipulating information from long term memory.

There have also been several data-driven approaches to identifying the sub-components of executive functioning (e.g., Friedman & Miyake, 2004; Huizinga, Dolan, & van der Molen,

2006; Hull, Martin, Beier, Lane, & Hamilton, 2008; Miyake et al., 2000). For example, using confirmatory factor analysis, Miyake et al. (2000) demonstrated that shifting (switching between tasks or mental sets), updating (working memory), and inhibition were clearly distinguishable in young adults, though they shared some underlying commonality. This suggests that these represent distinct aspects of cognitive functioning, but that there is a common executive control mechanism shared by all executive functions. The exact nature of this common factor has not yet been described. In a similar study, Hull et al. (2008) identified shifting and updating factors in older adults; however, the inhibition factor failed to emerge. The authors suggest two possibilities to explain this finding: first, a decline in inhibition abilities may account for the lack of cohesiveness among inhibition variables, and second, they did not include measures of resistance to interference, which has previously been found to load on an inhibition factor in older adults (Hedden & Yoon, 2006). However, though Hedden et al. (2006) found a separate component for resistance to interference, a distinct construct representing inhibition of prepotent responses did not emerge. The authors suggest that this could be due to the existence of multiple subcomponent processes within the construct of inhibitory control, less coherence amongst individual measures of inhibition, or the involvement of inhibitory functions in other subcomponents of executive functions.

Thus, shifting, updating, and inhibition appear to be robust subcomponents of executive functions, however they are not necessarily the only subcomponents. As previously mentioned, several other subcomponent processes have been proposed such as planning, organization, problem solving, self-monitoring, judgment, and abstraction (Alvarez & Emory, 2006; Diamond, 2013; Elliott, 2003; Gazzaley & D'Esposito, 2007; Royall et al., 2002; Stuss & Levine, 2002). However, the difficulty is that such complex functions are difficult to operationalize and test, and ultimately, intact executive functioning requires that several cognitive processes work together efficiently. In addition, executive tasks typically require a variety of other cognitive functions as well, thus performance on measures of executive function may be contaminated by deficits in non-executive cognitive domains.

1.4.1 Neurological correlates of executive function. There is a long history of research linking executive functions to the frontal lobes. Patients with focal lesions to the frontal lobes (particularly the dorsolateral prefrontal cortex) perform poorly on a variety of tasks of executive functioning and functional neuroimaging studies have consistently shown the activation of the

prefrontal cortex during the performance of tasks of executive function (for reviews, see Collette, Hogge, Salmon, & Van der Linden, 2006; Gazzaley & D'Esposito, 2007; Stuss & Levine, 2002). However, other brain areas are also activated during the performance of executive functioning tasks, and some patients with non-frontal lesions perform poorly on tests of executive function (Alvarez & Emory, 2006). It is now commonly believed that executive functions are not localized exclusively within the frontal lobes, but rather that intact executive functioning relies on a network of circuits connected to the prefrontal cortex (Gazzaley & D'Esposito, 2007; Royall et al., 2002). Indeed, the prefrontal cortex is a major target for both limbic and basal ganglia-thalamocortical circuits and it is connected with more brain areas than any other cortical region (Fuster, 2002; Royall et al., 2002). Furthermore, the unifying role of executive functions over lower level cognitive processes that are largely carried out in non-frontal brain areas would necessitate the coordination of multiple brain areas via neural networks.

Evidence supporting a distributed network model of executive functioning comes from studies of patient groups with executive dysfunction as well as from structural and functional neuroimaging studies. For example, PET studies in patients with Parkinson's disease have shown that tests of executive function are associated with abnormal function of the globus pallidus, but not the prefrontal cortex (Elliott, 2003). Thus, striatal dysfunction may disrupt frontal lobe functioning through the disruption of fronto-striatal networks. In a recent study by Burzynska et al. (2012), cortical thickness in both the lateral prefrontal cortex and the parietal cortex (specifically bilateral middle frontal gyrus, right inferior frontal gyrus, postcentral gyrus, precentral gyrus, and superior parietal gyrus) was found to be positively associated with performance on a task of executive functioning (Wisconsin Card Sorting Test). Numerous functional neuroimaging studies have found activation of the prefrontal cortex (dorsolateral, inferior, and anterior cingulate) as well as posterior regions (mainly in the parietal cortex) during the performance of various tasks of executive function including tasks of updating, shifting, inhibition, and dual task (for reviews, see Chung et al., 2014; Collette et al., 2006). Collette et al. (2005) examined the neural substrates of updating, shifting, and inhibition in a PET study using conjunction analysis. A global analysis of all the tasks used in their study demonstrated that there were certain areas that were commonly activated in all tasks of executive functioning, namely the right intraparietal sulcus, the left superior parietal gyrus, and the left lateral prefrontal cortex. They also demonstrated that each subcomponent of executive functioning examined was

associated with activation of specific prefrontal areas. Updating tasks were associated with the specific activation of the right superior frontal sulcus, left frontopolar cortex, and right inferior frontal sulcus in comparison to shifting tasks, and with the left intraparietal sulcus and frontopolar cortex in comparison to inhibition. Shifting tasks were associated with specific activation of the left intraparietal sulcus in comparison to inhibition. Finally, inhibition was associated with the specific activation of the right orbitofrontal gyrus in comparison to updating and with the right middle and superior frontal gyrus in comparison to shifting. These findings support both the unity and diversity of executive functions. The existence of common activation in several brain areas during multiple different executive tasks attests to a unifying factor common to all executive functions, whereas the existence of specific activation of certain areas for one subcomponent and not the others suggests that the subcomponents are somewhat separable. This is in agreement with the findings from the confirmatory factor analysis of Miyake et al. (2000), which suggested both specificity of the subcomponents and commonality between them.

The focus of this dissertation is on two important aspects of executive functioning, inhibitory control and working memory. These two processes are interrelated and often co-occur. For example, when engaging in goal-directed behaviour in which inhibition is needed, working memory is needed to know what is relevant and what needs to be inhibited. Conversely, when working with information held in mind, inhibitory control is needed to suppress irrelevant information and focus on the information to be manipulated. However, when developing tasks to assess working memory and inhibition, it is possible to minimize their effects on each other (e.g., minimize working memory requirements in a task of inhibition) (see Diamond, 2013 for a discussion of the interrelationship between inhibition and working memory). For the purposes of this review, the two processes will be considered separately, and each is discussed in detail below.

1.4.2 Inhibitory control. Inhibitory control involves the ability to "control one's attention, behaviour, thoughts, and/or emotions to override a strong internal predisposition or external lure, and instead do what's more appropriate or needed" (Diamond, 2013, p. 136). The ability to exert this control over our own behaviour is essential for enabling the choice of how to react, rather than being driven by impulses and habit. It allows us to delay gratification and behave in socially appropriate ways. Inhibitory control can be applied to attention to direct

voluntary attention to a particular stimulus based on goals or intentions. Cognitive inhibition can be used to suppress unwanted thoughts or interference from information that was presented at a different time. This dissertation will focus specifically on prepotent response inhibition, in which a dominant, automatic response must be inhibited (see Friedman & Miyake, 2004 for a discussion of the different aspects of inhibitory control).

Many different tasks have been used to measure inhibitory control, including the Stroop task, Hayling test, Go/No-go task, stop-signal task, Simon task, and flanker task (see Diamond, 2013 for a description of tasks of inhibitory control). The three measures of inhibitory control that will be examined here are the Stroop task, Hayling Test, and Go/No-go task. The Stroop task (Strauss, Sherman, & Spreen, 2006; Stroop, 1935) is a well-known task in which colour words are printed in an incongruent coloured ink (e.g., "green" printed in red ink). The participant must name the colour of the ink and inhibit the prepotent response of reading the word. This may be analogous to situations in daily life when we must overcome automated, routine behaviours, such as when you change your banking PIN and must inhibit the automated response of typing in the old PIN when making a purchase. In the Hayling Test (Burgess & Shallice, 1997), sentences with the last word missing are read to participants, and the participant must provide a word that does *not* fit at the end of the sentence. For example, in completing the sentence "Most cats see very well at…" the participant must inhibit the verbal response "night" and instead provide an unrelated word, such as "pencil". This task can be likened to everyday situations in which one must inhibit saying the first thing that comes to mind, which could be embarrassing or hurtful to others.

The Go/No-go task is different from the Stroop task and Hayling Test in at least one important way. The Stroop task and Hayling Test both require the inhibition of a prepotent response as well as the generation of an alternate response. In contrast, the Go/No-go task requires participants to press a button in response to a stimulus and to simply inhibit the response and do nothing in response to a different stimulus. The stimulus requiring a response ("Go" trials) usually occurs much more frequently than the stimulus requiring the inhibition of a response ("No-go" trials), thus creating a prepotent response of pressing the button that must be inhibited on the less frequent No-go trials. This task may be analogous to real-world situations in which an action is checked just before completing it. For example, if you are playing catch in

a park and a child runs in front of you, you must inhibit yourself from completing the action of throwing the ball.

Several functional neuroimaging studies have examined the neural correlates of response inhibition and demonstrated that these tasks are associated with activation of the dorsomedial prefrontal cortex, lateral prefrontal cortex, parietal cortex, insular cortex, bilateral precuneus, left angular gyrus, and right middle temporal gyrus (e.g., Blasi et al., 2006; Boehler, Appelbaum, Krebs, Hopf, & Woldorff, 2010; Rubia, Smith, Taylor, & Brammer, 2007; see Chung et al., 2014 for a review). For example, Blasi et al. (2006) demonstrated that the dorsolateral prefrontal cortex (DLPFC), ventrolateral prefrontal cortex (VLPFC), and parietal cortex were activated to a greater degree for response inhibition tasks, whereas the dorsal anterior cingulate cortex was activated to a greater degree for interference monitoring and suppression. Others have also argued that the anterior cingulate is involved in conflict monitoring, detection, and resolution (Kerns et al., 2004; Van Veen & Carter, 2002).

The Stroop task has been investigated in several functional neuroimaging studies. For example, fMRI studies have reported increased activation in the inhibition condition mostly in the anterior cingulate and left DLPFC (Banich et al., 2000; Fan, Flombaum, McCandliss, Thomas, & Posner, 2003; MacDonald, Cohen, Stenger, & Carter, 2000; Milham et al., 2001). A recent meta-analysis of functional neuroimaging studies (Nee, Wager, & Jonides, 2007) found that the most significant clusters for activation on the Stroop task were the left DLPFC (extending to the insula), the left medial prefrontal cortex (including the anterior cingulate), and the left posterior parietal cortex. The Go/No-go task was also examined in this meta-analysis, and the most prominent cluster for this task was the right DLPFC (extending to the inferior frontal gyrus and insula). Additional significant clusters were found in the left DLPFC, anterior cingulate, and right posterior parietal cortex. Another meta-analysis of Go/No-go studies (Swick, Ashley, & Turken, 2011) reported major clusters in the right insula, right middle frontal gyrus, right inferior parietal lobule/precuneus, and the superior frontal gyrus, with additional significant clusters in the left middle and inferior frontal gyri and the left insula. Finally, the neural substrates of the Hayling Test were investigated in a PET study by Collette et al. (2001). In this study, the inhibition condition produced increased activation of the bilateral middle frontal gyrus, bilateral inferior frontal gyrus, and left orbitofrontal cortex in comparison to the initiation (control) condition. Overall, tasks of response inhibition appear to involve

predominately the DLPFC, anterior cingulate, and the posterior parietal cortex, suggesting the involvement of a fronto-parietal network underlying these functions.

1.4.3 Working memory. Working memory is defined as the ability to manipulate information that is held in mind (Baddeley, 1992; Diamond, 2013). This ability is critical for coping with anything in life that unfolds over time, such as tracking written or spoken language, as well as for working with multiple pieces of information such as when formulating a plan or considering relationships between ideas or items. Working memory can be distinguished from short-term memory, which entails holding information in mind without manipulation. In Baddeley et al.'s multi-component model of working memory (2003), the central executive component of working memory manipulates information and creates new representations of information activated by the phonological loop, visuospatial sketchpad, or episodic buffer.

Some tasks used to measure working memory include Digit Span Backwards, Letter-Number Sequencing, N-back tasks, the Self-Ordered Pointing task, and the Corsi Block test (see Diamond, 2013 for a description of working memory tasks). In the Digit Span Backwards task (Wechsler, 1997), randomly ordered digits are presented verbally, and the participant must repeat the numbers in the backwards order. The Letter-Number Sequencing task (Wechsler, 1997) is somewhat more complicated. In this task, intermixed letters and numbers are presented verbally, and the participants must repeat back the numbers and letters in sequential order, beginning with the numbers and followed by the letters. Both of these tasks require holding a limited amount of information in mind and manipulating the content. In contrast, the N-back task requires participants to hold information in mind and continually update that information as new stimuli are presented. In this type of task, the participant must make a forced-choice decision for each stimulus presented as to whether or not it is a match for the stimulus presented *n* trials back. The working memory load can be manipulated by requiring the participant to compare the current stimulus to the one presented in the previous trial (1-back), to the stimulus presented two trials before (2-back), or to the stimulus presented three trials back (3-back). This task is considered to be a task of working memory since the contents held in mind are continually updated, rather than simply maintaining static information.

Functional neuroimaging studies indicate that the VLPFC is activated during retrieval and maintenance of representations. In contrast, the DLPFC is involved in monitoring and manipulation of the representations maintained in the VLPFC (Elliott, 2003). Baddeley et al.

(2003) propose that the different components of working memory are localized in different brain areas. Specifically, lesion and functional neuroimaging studies have demonstrated that the functions of the phonological loop are localized in the left temporoparietal regions. In contrast, the functions of the visuospatial sketchpad are primarily localized in the right inferior parietal cortex, right premotor cortex, and right inferior frontal cortex. It is suggested that the central executive component of working memory is localized primarily within the bilateral DLPFC (Baddeley, 2003; Huntley & Howard, 2010). Thus, a fronto-parietal network is thought to underlie tasks of working memory, which is left-lateralized in the verbal domain and right-lateralized in the visual domain. Recent evidence suggests a dissociation between the contributions of the prefrontal cortex and posterior parietal cortex to working memory tasks, namely that the prefrontal cortex is primarily involved in monitoring the contents of working memory, whereas the parietal cortex is involved primarily in manipulation of information held in mind (Champod & Petrides, 2010).

The neural underpinnings of working memory have most commonly been investigated using the N-back task. Numerous studies have consistently reported activation of the DLPFC, VLPFC, supplementary motor area, premotor cortex, and posterior parietal areas during working memory tasks such as the N-back task, and this activation has been found to increase with higher working memory load (for reviews, see Baddeley, 2003; Chung et al., 2014; Collette et al., 2006; D'Esposito et al., 1998; Elliott, 2003; for a meta-analysis, see Owen, McMillan, Laird, & Bullmore, 2005). In addition, several studies have examined functional connectivity during the N-back task using fMRI, and fronto-parietal connectivity has been found to increase as a function of working memory load (Honey et al., 2002; Narayanan et al., 2005; Newton, Morgan, Rogers, & Gore, 2011). Thus, as with response inhibition, working memory tasks appear to rely on a distributed fronto-parietal cortical network.

1.4.4 Executive functioning in Alzheimer's disease. Patients with AD are impaired on a wide variety of executive functioning tasks and these deficits present early in the course of the disease (Perry & Hodges, 1999; Weintraub et al., 2012). For example, impairments have been reported on measures of cognitive flexibility such as the Trail Making Test (Ashendorf et al., 2008; T.-F. Chen et al., 2009; Coubard et al., 2011; Lafleche & Albert, 1995; Lonie, Tierney, et al., 2009b) and the Wisconsin Card Sorting Test (Bondi, Monsch, Butters, Salmon, & Paulsen, 1993; T.-F. Chen et al., 2009; Stokholm, Vogel, Gade, & Waldemar, 2006), as well as on

measures of planning and organization such as the Tower of London and the Self-Ordered Pointing Task (Collette, Van der Linden, & Salmon, 1999; Coubard et al., 2011; Franceschi et al., 2007; Lange, Sahakian, Quinn, Marsden, & Robbins, 1995; Rainville et al., 2002). Impairments have also been observed on phonemic verbal fluency tests, which require initiation and maintenance of word generation in an organized fashion as well as inhibition and shifting abilities (T.-F. Chen et al., 2009; Collette et al., 1999; Coubard et al., 2011; Lafleche & Albert, 1995; Rinehardt et al., 2014; Stokholm et al., 2006).

Measures of inhibitory control have also been found to be impaired in AD (for a review, see Amieva, Phillips, Sala, & Henry, 2004). For example, impairments have been reported on the Stroop task (Amieva et al., 2002; Bondi et al., 2002; Collette et al., 2007; Fisher, Freed, & Corkin, 1990; Perry & Hodges, 1999; Spieler, Balota, & Faust, 1996; Stokholm et al., 2006; Vasconcelos et al., 2014; however, see Coubard et al., 2011), and a meta-analysis found that AD patients demonstrated a larger effect on the inhibition condition of the Stroop relative to the baseline condition (Amieva et al., 2004), indicating that the deficit on the Stroop cannot be explained by speed of information processing alone. This finding was replicated by Ben-David et al. (2014) who performed a meta-analysis that demonstrated that there was a significant increase in the Stroop effect in AD patients and that speed of information processing only accounted for 25% of the variance in this effect. However, they also found a disproportionate deficit in colour naming in comparison to word reading, which accounted for a significant amount of the variance in the inhibition condition, suggesting that sensory factors may also play an important role in poor performance on this task. In support of a deficit in inhibitory processes, Collette et al. (1999) also found that deficits in inhibition cannot be explained by deficits in processing speed using a task that does not require additional sensory processes in the inhibition condition. They found that AD patients produced significantly more semantically related content on the inhibition condition of the Hayling Test, but did not demonstrate an increase in speed of responding. This result was replicated by Belleville et al. (2007), and increased errors on the Hayling Test was also reported by Nash et al. (2007).

However, there is some evidence that not all inhibitory mechanisms are uniformly impaired. On a Go/No-go task, Amieva et al. (2002) and Collette et al. (2007) found longer reaction times on Go trials, but no difference on the number of No-go errors. In both of these studies, however, 50% of trials were Go trials, creating a relatively weak reinforcement of the

response to go trials, and thus making less of a demand on inhibitory functions. It is possible that a Go/No-go task that places a larger demand on inhibitory processes may demonstrate impairment on this type of task in AD patients.

A number of studies have demonstrated that the central executive component of working memory is impaired in the early stages of the AD, as is evidenced by impairments on tasks such as alphabet span tasks and the Brown-Peterson task (Belleville et al., 2007; Belleville, Rouleau, Van der Linden, & Collette, 2003; Collette, 1999; Huntley & Howard, 2010; Sebastian, Menor, & Elosua, 2006) as well as the N-back task (Lim et al., 2008; Rombouts, Barkhof, Goekoop, Stam, & Scheltens, 2005; Waltz et al., 2004). Impairments have also been reported on Digit Span Backward and Letter-Number Sequencing tasks (Kessels, Molleman, & Oosterman, 2011; Toepper, Beblo, Thomas, & Driessen, 2008; Vasconcelos et al., 2014; however, see Perry et al., 2000).

Stokholm et al. (2006) examined the frequency of impairment (defined as a z-score greater than 2 SD below that of controls) in patients with very mild AD (MMSE score of 24-29) on a variety of executive function tasks. They examined the Trail Making Test, Stroop task, Wisconsin Card Sorting Test, verbal fluency, design fluency, and Similarities subtest and found that executive dysfunction was common, with 76% of patients demonstrating impairment on at least one of the measures tested. The most frequent impairments were observed on the Trail Making Test (47%), Stroop task (42%), and verbal fluency task (36%), whereas impairment was much less common on the Wisconsin Card Sorting Test (6%), design fluency (3%), and Similarities subtest (11%). Working memory is also frequently impaired, as demonstrated by Belleville et al. (2007), who reported that 75% of the patients were impaired on the Brown-Peterson task.

1.4.5 Executive functioning in mild cognitive impairment. Longitudinal studies have shown that individuals who go on to develop AD show executive deficits even during the preclinical phase. For example, Albert et al. (2007) followed individuals who were cognitively normal or had MCI at baseline over four years and found that those who converted to AD during that time period had lower scores on executive functioning measures at baseline. Similar results have been reported in other longitudinal studies (e.g., P. Chen et al., 2001; Perri, Serra, Carlesimo, Caltagirone, Early Diagnosis Group of Italian Interdisciplinary Network on Alzheimer's Disease, 2007) as well as in a meta-analysis of such studies (Bäckman, Jones,

Berger, Laukka, & Small, 2005). Furthermore, the effect size of executive dysfunction reported in the meta-analysis was approximately equal to the effect size for the episodic memory deficit (d =1.07 for executive function and d = 1.03 for episodic memory). These findings suggest that executive dysfunction may be as important as episodic memory deficits in the early diagnosis of AD.

Recent studies are increasingly demonstrating that impairment in multiple cognitive domains is common in MCI (Bäckman, Jones, Berger, Laukka, & Small, 2004; Loewenstein et al., 2006; Nordlund et al., 2005) and that progression to dementia is much more common in individuals with multiple deficits (Alexopoulos, Grimmer, Perneczky, Domes, & Kurz, 2006; Aretouli, Tsilidis, & Brandt, 2013; Bozoki, Giordani, Heidebrink, Berent, & Foster, 2001; Loewenstein et al., 2009). Executive functions appear to be a domain that is frequently impaired in MCI. For example, Johns et al. (2012) examined multiple subcomponents of executive function in aMCI and found that all of the patients were impaired (z-scores of greater than 1.0 SD below the mean of controls) on at least one measure of executive function. Inhibitory control was the domain most frequently and severely impaired, with over 90% of patients demonstrating impairment on the Hayling Test. Impairment was also common for the other subcomponents examined (approximately 90% for verbal fluency and Tower of London, and between 50% and 70% on the Stroop task, Brown-Peterson Task, and Letter-Number Sequencing task). When the criterion for impairment was set at 1.5 standard deviations below the mean of controls, the frequency of impairment remained the same on the Hayling Test, and changed very little on the other tests (with the exception of verbal fluency, which decreased to approximately 60% and the Stroop task, which decreased to approximately 30%). Similar results were reported by Belleville et al. (2007), though fewer of the patients in their sample were impaired on the Hayling Test (approximately one third were impaired on the Hayling Test, but three quarters were impaired on the Brown-Peterson Task). In this study, ninety percent of MCI patients were impaired on at least one of the three measures.

Despite the increasing evidence that executive dysfunction is common in aMCI, the literature is far from unanimous on the topic (for a review, see the appendix of Johns et al., 2012). Several studies have reported deficits on various measures of executive function such as the Trail Making Test (N.-C. Chen et al., 2013b; T.-F. Chen et al., 2009; Kessels et al., 2011; Lopez et al., 2006; S. E. Price et al., 2010), Wisconsin Card Sorting Test (Ballesteros, Mayas, & Reales,

2013; Borkowska, Drozdz, Jurkowski, & Rybakowski, 2009; T.-F. Chen et al., 2009; Peltsch, Hemraj, Garcia, & Munoz, 2014), tower tasks (Brandt et al., 2009; Johns et al., 2012), and phonemic verbal fluency (T.-F. Chen et al., 2009; Lopez et al., 2006; Muangpaisan, Intalapaporn, & Assantachai, 2010; Rinehardt et al., 2014). However, many studies have reported no deficit on the same measures: Trail Making Test (Lonie, Tierney, et al., 2009b), Wisconsin Card Sorting Test (Nordlund et al., 2005; Olson et al., 2008), phonemic verbal fluency (Kramer et al., 2006; Lonie, Herrmann, et al., 2009a; Nordlund et al., 2005; N. A. Phillips, Chertkow, Leblanc, Pim, & Murtha, 2004). As previously mentioned, there is some evidence that inhibitory control and working memory may be particularly affected in MCI (Belleville et al., 2007; Johns et al., 2012). However, findings in these domains are also mixed. For example, deficits have been reported on the Stroop task (Bélanger, Belleville, & Gauthier, 2010; T.-F. Chen et al., 2009; Kramer et al., 2006; Peltsch et al., 2014), Hayling Test (Bélanger et al., 2010; Bélanger & Belleville, 2009; Brandt et al., 2009; Johns et al., 2012), and Go/No-go task (Cid-Fernández, Lindín, & Díaz, 2014; Dwolatzky et al., 2003; Zihl, Reppermund, Thum, & Unger, 2010), but other studies have also reported no deficit on these tasks [Stroop (Lopez et al., 2006; Nordlund et al., 2005; D. Zheng et al., 2012), Hayling (Belleville et al., 2007; Bisiacchi, Borella, Bergamaschi, Carretti, & Mondini, 2008), Go/No-go (Y. Zhang, Han, Verhaeghen, & Nilsson, 2007)]. Deficits on tests of working memory are more consistently reported, for example on the Brown-Peterson Task (Belleville et al., 2007; Johns et al., 2012), N-back tasks (Borkowska et al., 2009; Guild et al., 2014; Rombouts et al., 2005; D. Zheng et al., 2012), Digit Span Backward (Chang et al., 2010; Crowell, Luis, Vanderploeg, Schinka, & Mullan, 2002; Kessels et al., 2011; Muangpaisan et al., 2010), and Letter-Number Sequencing (Kessels et al., 2011); however, a few studies have reported no deficit on working memory tasks [alphabet span (Belleville et al., 2007), Digit Span Backward (N.-C. Chen et al., 2013b; Kramer et al., 2006; Lopez et al., 2006)]. This type of inconsistency in findings is commonly seen when comparing multiple studies examining MCI, and it may be due to the heterogeneous nature of MCI, as well as differences in recruitment and testing procedures. Furthermore, the subtle cognitive deficits present in MCI are likely more difficult to detect consistently than the more pronounced deficits seen in AD.

Nevertheless, the presence of executive deficits in MCI, in addition to deficits in episodic memory, semantic memory, and visual perception, increases the sensitivity and specificity of

prediction of conversion to dementia (Belleville, Gauthier, Lepage, Kergoat, & Gilbert, 2014; Chapman et al., 2011). In a longitudinal study by Balota et al. (2010), Stroop errors was the strongest discriminator in predicting conversion to dementia in a sample of healthy older adults. Stroop performance also predicts the presence of preclinical pathology as measured by cerebrospinal fluid beta amyloid$_{42}$/tau ratios (Harrington et al., 2013). Similarly, Aretouli et al. (2013) investigated the question of whether performance on measures of executive function in MCI can predict conversion to dementia over a period of four years using 18 different tests of executive function. They found that eight of these tests were individually associated with conversion, including all three of the measures of inhibition. However, when other demographic, clinical, and non-executive cognitive variables were considered, only the Hayling Test showed a trend towards an association with MCI outcome. This is consistent with previous findings that semantic inhibition is particularly impaired in aMCI, with the z-score on the Hayling test ($z = -7.2$) being similar to the z-score for episodic memory ($z = -6.3$) (Johns et al., 2012).

Overall, despite inconsistencies in the literature, it is clear that executive dysfunction can be detected in early AD, preclinical AD, and MCI. However, the neural correlates of these deficits remain unclear, though the prevailing view is that disruption of neuronal networks plays an important role (Bokde et al., 2009; Delbeuck et al., 2003; D. P. Salmon & Bondi, 2009). The following section will review findings on the neural correlates of executive dysfunction in MCI and AD with a special emphasis on studies examining EEG coherence.

1.5 Neural Correlates of Executive Functioning in MCI and AD

The neurological underpinnings of executive dysfunction in MCI and AD remain unclear. However, the lack of clear frontal lobe atrophy in the early stages of the disease suggests that these deficits may arise from a disruption of neural networks supporting executive functioning. Recent structural neuroimaging studies that have explored the relationship between neuropathology and cognition in AD and MCI have typically found that executive functioning is associated with broad measures of neuropathology, such as whole-brain atrophy, ventricular enlargement, and cortical thickness in multiple brain regions (Braskie & Thompson, 2013; Chang et al., 2010; Vasconcelos et al., 2014) as well as changes in white matter (T.-F. Chen et al., 2009; Maillard et al., 2012; Marra, Ferraccioli, Vita, Quaranta, & Gainotti, 2011; Reijmer et al., 2013). In a study that examined the relationship between Stroop performance and amyloid plaques and neurofibrillary tangles at autopsy, there was a relationship between the interference

score on the Stroop and neurofibrillary tangles in the hippocampus and superior temporal cortex (Bondi et al., 2002). No association was found with tangles in the inferior parietal cortex or midfrontal cortex or with amyloid plaques in any of the four regions examined.

Functional neuroimaging studies in MCI and AD have produced variable results. For example, reduced activation has been reported in frontal and parietal regions in MCI patients during a visuospatial working memory task (Alichniewicz, Brunner, Klünemann, & Greenlee, 2012), whereas increased frontal and parietal activation has been reported during the Stroop task (C. Li, Zheng, Wang, Gui, & Li, 2009). There is some evidence that compensatory increases in activation may occur in the early stages of MCI, but that during the later stages, compensatory increases are no longer present and decreases in activation may begin to appear. Clément et al. (2013) examined fMRI activation during the performance of manipulation and divided attention tasks in early- and late-stage MCI patients and found increased activation in early-stage MCI patients in mainly prefrontal regions during the manipulation task and in a fronto-striatal network during the divided attention task. This increased frontal activation was associated with better performance on executive tasks; however, MCI patients did exhibit a deficit on task performance in comparison to controls. In contrast, late-stage MCI patients exhibited hypoactivation of prefrontal and occipito-temporal areas during the performance of the manipulation task and there were no differences in activation between late-stage MCI patients and controls on the divided attention task. In addition, there were no significant correlations between cognitive performance and activation in the late-stage MCI group. Thus, compensatory increases in activation may be present in the earliest stages of the illness, with a breakdown of these processes occurring as the disease progresses.

In AD patients, decreased frontal activation in conjunction with increased parietal activation has been observed during the performance of the N-back task of working memory (Lim et al., 2008) and decreased prefrontal activation has been observed during the Stroop task (C. Li et al., 2009). Furthermore, both MCI patients and AD patients show decreased deactivation of the default mode network during the performance of the N-back task, with deactivations in MCI patients being intermediate between controls and AD patients for anterior frontal regions and similar to AD patients in the precuneus (Rombouts et al., 2005).

Collette et al. (1999) examined the relationship between executive dysfunction and cerebral metabolism at rest in AD. They found a positive correlation between a factor

representing inhibitory control and metabolism in the middle and superior frontal gyrus. In contrast, a factor representing working memory was associated with metabolism in the posterior cingulate, middle temporal region, and parietal areas. In a recent study, a composite executive functioning score was associated with hypometabolism in parietal and temporal regions, but not frontal regions in both MCI and AD patients (Habeck et al., 2012). However, frontal metabolism in addition to parietal and temporal metabolism has been associated with performance on other executive tasks, such as the clock drawing task (Shon et al., 2013), the Stroop task (Yun et al., 2011), dual task performance (Laine et al., 2009), and measures of abstract reasoning, fluency, and planning (Woo et al., 2010). Thus, both frontal and non-frontal (particularly in temporo-parietal) regions appear to be involved in executive functioning in MCI and AD. However, frontal dysfunction does not appear to be necessary to produce executive dysfunction in these groups. This was demonstrated by Collette et al. (Collette, Van der Linden, Delrue, & Salmon, 2002), who examined two groups of AD patients: those with hypometabolism restricted to parietal and temporal regions and those with both frontal and posterior hypometabolism. They examined their performance on a variety of executive tasks including tasks of inhibitory control, verbal fluency, and selective attention, and they found that AD patients in both groups performed worse than controls on all of the executive tasks, whether frontal hypometabolism was present or not. Once again, this is evidence supporting the hypothesis that executive dysfunction in AD may be a consequence of disconnection between anterior and posterior regions.

The relationship between brain functioning and cognitive functioning may continue to change as the disease progresses. Bracco et al. (2007) examined the metabolic correlates of executive functioning in mild and very mild AD and found that executive measures were associated with prefrontal metabolism in very mild AD patients, whereas parietal, temporal, and occipital areas were more strongly associated with executive measures in the mild AD patients. Thus, the relationship between cognition and brain functioning in MCI and AD is complex and depends on a variety of factors. For example, the stage of the illness may play an important role, with potentially significant differences in the association between brain and cognitive function even within diagnostic groups. Furthermore, individual differences in neurocognitive reserve and successful or unsuccessful neural compensation mechanisms may also play an important role. However, overall, the present state of the literature points to the importance of neural networks connected with the frontal lobes in supporting executive functioning and that disruption of these

networks is related to executive dysfunction in MCI and AD. The disconnection hypothesis can be more directly tested using EEG coherence, which is particularly useful for exploring network functioning, given the high temporal resolution of the EEG signal.

1.6 EEG Coherence

It is now generally accepted that several different brain regions must cooperate in the performance of any brain function (Başar, Başar-Eroğlu, Güntekin, & Yener, 2013). Therefore, the analysis of functional networks is extremely important for advancing our understanding of normal and pathological brain functioning. EEG coherence is a representation of the functional interaction between two brain regions (Nunez & Srinivasan, 2006; Nunez et al., 1997). It is a measure of the consistency over time of the EEG signal between pairs of electrodes placed on the scalp; thus, the phase or voltage of the two signals being examined may be the same or different, but if the difference tends to remain constant, then coherence will be high. Coherence is a linear measure of the covariance between two signals derived from the spectral decomposition of the EEG, for a given frequency range (Roach & Mathalon, 2008). The calculation of EEG coherence is analogous to the calculation of the Pearson product-moment correlation coefficient, and the resulting coherence value is analogous to the squared Pearson correlation. As such, coherence reflects the proportion of variance of channel 1 that can be accounted for by a constant linear transformation of channel 2 (Roach & Mathalon, 2008; Srinivasan, Winter, Ding, & Nunez, 2007). Increases in EEG coherence between two brain regions can be interpreted as representing some commonality in the generator(s) driving the two areas. One region may drive the other, they may mutually drive each other, or the two regions may be driven by a common third generator (Başar et al., 2013).

The calculation of coherence uses the following formula for segment number i, fixed frequency f, and fixed channel c:

$$Coh(c_1, c_2)(f) = | CS(c_1, c_2)(f) |^2 / (| CS(c_1, c_1)(f) | | CS(c_2, c_2)(f) |),$$

where $CS(c_1, c_2)(f) = \Sigma\, c_{1,\,i}\,(f)\; c_{2,\,i}\,(f)$

The numerator contains the cross-spectrum of two EEG signals c_1 and c_2 ($CS(c_1, c_2)$) for a given frequency bin (f) and the denominator contains the autospectra for c_1 ($CS(c_1, c_1)$) and c_2 ($CS(c_2, c_2)$) (Nunez & Srinivasan, 2006; Pfurtscheller & Andrew, 1999).

Coherence is sensitive to both magnitude and phase angle, though the coherence value is more strongly influenced by phase (Nunez & Srinivasan, 2006; Srinivasan et al., 2007).

Spontaneous coherence can be calculated by recording several minutes of continuous EEG data, sub-dividing into shorter segments and averaging across these segments, thus measuring the consistency of the relationship across multiple segments. In contrast, event-related coherence is calculated using segments locked to an event or task that is repeated a number of times, and all task-related trials are averaged together (Andrew & Pfurtscheller, 1996; Pfurtscheller & Andrew, 1999).

The calculation of coherence is done for specific frequency ranges. Frequency bands commonly examined include delta (0.5-3.5 Hz), theta (3.5-7.5 Hz), alpha (7.5-12.5 Hz), beta (7.5-30 Hz) and low gamma (30-60 Hz). The psychophysiological significance of EEG rhythms in the various frequency bands is still not fully understood (Niedermeyer, 2005); however, we do have some basic information about the nature of these rhythms. Generally speaking, delta and theta rhythms are characteristic of deep sleep, and high theta activity in the awake adult is associated with brain disorders such as epilepsy. However, rhythmic theta over the frontal midline region has also been associated with mental activity (e.g., problem solving) as well as drowsiness. Alpha rhythms appear spontaneously during a wakeful, relaxed state during mental inactivity, and are most prominent at occipital sites when the eyes are closed. Beta rhythms are enhanced when performing mental calculations and during a state of expectancy or tension. Finally, low gamma rhythms have been associated with various sensory and cognitive processes, including perception and attention (Freeman & Quiroga, 2013; Niedermeyer, 2005). Changes in EEG coherence across frequency bands may also be relevant to cognitive functioning, which is discussed in greater detail below.

1.7 EEG Coherence and Executive Functioning

There has been an increasing number of studies examining the neural substrates of executive functioning using EEG coherence in recent years, most notably in the area of working memory. There are also some studies examining more broad-spectrum measures of executive functioning, such as maze tasks (Tremblay et al., 1994) and card sorting tasks (Carrillo-de-la-Peña & García-Larrea, 2007). Tremblay et al. (1994) measured EEG coherence during the performance of five maze tasks, which required a complex set of skills including visual perception, nonverbal reasoning, and planning. They also measured coherence during a modified maze task, in which participants merely traced a line showing the direct way out of the maze. When compared to the modified maze task, coherence during the maze task was increased

between posterior sites (parietal, temporal occipital) in the theta band and between left frontal and other frontal, temporal and occipital sites in the high beta band. In contrast, decreases in coherence were observed in the alpha band between frontal and parieto-central sites, and in the low beta band between frontal and central sites.

In a more recent study, Carrillo-de-la-Peña and García-Larrea (2007) measured EEG coherence during the performance of a computerized version of the Wisconsin Card Sorting Test. They compared coherence values for good vs. bad performers (defined as participants who failed to complete the six categories) specifically for local frontal and local parietal electrode pairs. They found lower frontal coherence in bad performers in the alpha and beta bands, and coherence values in these bands were negatively correlated with the number of errors on the task. In contrast, there was no significant difference between groups for parietal coherence and no correlations between parietal coherence and task performance. Thus, increased frontal coherence appears to support good performance on the Wisconsin Card Sorting task; however, the authors did not examine coherence between frontal and posterior regions. Cocchi et al. (2011) examined coherence during the performance of a dual task (simple visual perception task and visuospatial short term memory task with low and high memory loads) in the alpha, beta, and gamma bands. They found that for dual task in comparison to single task, coherence in dorsofrontal-occipital connections increased in the beta band, and prefrontal-occipital and prefrontal-parietal connections increased in the gamma band.

A large study by Paul et al. (2005) specifically examined gamma band phase synchrony at frontal sites across development in 550 individuals from age 11 to 70. They measured phase synchrony during the performance of an auditory oddball task, and participants also completed two measures of executive functioning (trail making test and maze task). They found that performance on measures of executive functioning declined with age (particularly in individuals over 50 years of age) and that left frontal gamma synchrony increased with age. Furthermore, there were modest negative correlations between frontal gamma synchrony and executive task performance. This study suggests that the relationship between synchrony between brain regions and cognitive performance is complex, and that different patterns of relationships may emerge in different groups of participants, such as in normal aging. However, in this study, EEG was not recorded during the performance of an executive task, and it is possible that a different pattern

would emerge when examining brain functioning during executive task performance or during a resting state.

Overall, it is difficult to draw conclusions on the relationship between EEG coherence and broad-spectrum measures of executive functioning on the basis of the current literature. Few studies have been conducted, and the methods vary widely in terms of the tasks used, the manner in which coherence was measured during task performance, which frequency bands and electrode pairs were examined, and whether coherence during the task was compared to a baseline task, compared between groups, correlated with performance. However, these studies do suggest that the performance of an executive task induces increased coherence in comparison to a baseline task (Cocchi et al., 2011; Tremblay et al., 1994), possibly between frontal and fronto-posterior sites in higher frequency bands (Cocchi et al., 2011; Tremblay et al., 1994) and between posterior sites in lower frequency bands (Tremblay et al., 1994). Furthermore, higher coherence appears to be related to better task performance in younger adults (Carrillo-de-la-Peña & García-Larrea, 2007; Cocchi et al., 2011), but this pattern may not hold true for older adults (Paul et al., 2005).

1.7.1 EEG coherence and inhibitory control. Several studies have examined EEG coherence during Go/No-go tasks with an equal proportion of Go and No-go trials (Harmony, Alba, Marroquín, & González-Frankenberger, 2009; Müller & Anokhin, 2012; Shibata et al., 1997; 1998). This type of task requires motor inhibition; however, due to the lack of a strong prepotent response, executive processes are not thought to play a strong role. The most commonly reported finding in these studies is a increase in theta synchrony between anterior and posterior regions (Harmony et al., 2009; Shibata et al., 1998) and between local frontal and interhemispheric frontal regions (Müller & Anokhin, 2012; Shibata et al., 1997; 1998) for No-go trials in comparison to Go trials. Variable results have been reported for the alpha, beta, and gamma bands, with reported increases, decreases, or no differences (Harmony et al., 2009; Shibata et al., 1997; 1998).

One study that examined inhibitory control using a Go/No-go task with a higher Go trial to No-go trial ratio, similar to the paradigm used in this thesis, also found increased coherence in the theta band for No-go trials, specifically between fronto-polar and premotor areas (Brier et al., 2010). However, in this study, the delta, beta, and gamma frequency bands were not examined. In a study using a visual oddball task, in which an infrequent stimulus required a different

response from a frequent stimulus, the oddball stimulus generated higher delta and theta coherence for frontal, fronto-central, and fronto-parietal pairs, whereas the frequent stimulus generated higher coherence for the same pairs in the gamma band (Qassim, Cutmore, James, & Rowlands, 2013). The authors suggest that higher coherence in the lower frequency bands represents decision making and response processes, whereas higher gamma coherence reflects expectancy and preparation for the occurrence of an oddball.

EEG coherence has also been investigated during the performance of the Stroop task. In contrast to the findings reported with the Go/No-go task, Schack et al. (1999) reported that coherence values in the low beta band discriminated best between congruent and incongruent Stroop trials. The effect was lateralized, with coherence in the left hemisphere between frontal, fronto-parietal, and parieto-temporal-occipital regions being higher for incongruent trials and right hemisphere frontal coherence being higher for congruent trials. Liu et al. (2006) confirmed the sensitivity of the low beta band in the discrimination between congruent and incongruent trials; however, they did not find an effect of lateralization. Coherence within frontal, central, and parietal regions, as well as between frontal and parietal regions was higher for incongruent trials than for congruent trials.

Thus, overall, it appears that tasks that require inhibitory control elicit an increase in coherence within frontal and between frontal and posterior regions. However, the specific type of task employed may influence the frequency band in which these differences are observed.

1.7.2 EEG coherence and working memory. Studies that have examined EEG coherence during the performance of short-term memory tasks such as the Sternberg task or delayed choice reaction time tasks have reported increased coherence between frontal and posterior (temporal, parietal, occipital) regions in comparison to simple perception tasks in the theta band (Payne & Kounios, 2009; Sarnthein, Petsche, Rappelsberger, Shaw, & Stein, 1998), beta band (C. Babiloni, Babiloni, et al., 2004a), and gamma band (C. Babiloni, Babiloni, et al., 2004a; Lutzenberger, Ripper, Busse, Birbaumer, & Kaiser, 2002) as well as increased posterior coherence (parieto-temporal) in the alpha band (Payne & Kounios, 2009). Increased coherence in these regions in the theta and alpha bands have also been shown to be modulated by increasing memory load (Jensen & Tesche, 2002; Payne & Kounios, 2009).

Sauseng et al. (2005) conducted a study in which they manipulated the executive aspect of working memory. Participants were required to encode eight images of black bars on a white

background along with a verbal label (the number one through eight) prior to the EEG recording. The patterns varied on a number of dimensions (number, width, length, and orientation of bars). During the EEG recording, participants were presented sequentially with two verbal labels, and were required to retrieve the appropriate image and hold it in mind. Following this, participants were presented with a word indicating the dimension on which to compare the two images, and provide a verbal response as to which pattern was larger on that dimension. Thus, they compared a simple retrieval condition to an executive condition in which participants were required to manipulate and compare the two patterns held in mind. Results indicated an increase in theta coherence between frontal and posterior sites (parietal, temporal, occipital), as well as between cross-hemisphere temporal and parietal sites for the executive condition in comparison to the simple retrieval condition. In addition, there was a decrease in alpha coherence between frontal and fronto-central sites in the executive condition.

In another set of studies examining mental manipulation in working memory, Mizuhara et al. (2007; 2005) found increased phase synchronization during a mental arithmetic task in comparison to a resting condition in the theta band for frontal and fronto-parietal pairs, and in the beta band for parietal and fronto-parietal pairs. In addition, decreased synchronization in the alpha band was observed. Furthermore, correlations with fMRI activation in predominantly attentional areas (e.g., superior parietal lobule) for beta synchronization and with predominantly executive areas (e.g., DLPFC) for theta synchronization led the authors to the interpretation that beta synchronization represents attentional mechanisms, whereas theta synchronization represents the executive aspects of working memory.

Kawasaki et al. (2010; 2014) examined phase synchronization during auditory-verbal and visuo-spatial mental manipulation tasks. Participants either heard a number or a saw a dot on a screen. Following a retention period, participants were given an instruction for the manipulation of the number or the dot through addition of another number or moving the position of the dot in their mental representation, and were required to perform four manipulations for each stimulus. They were then presented with a probe, and were required to indicate whether or not the probe matched the manipulated stimulus. Participants completed five conditions: one auditory-verbal only, one visuo-spatial only, two dual task sequential (in which both auditory-verbal and visuo-spatial stimuli were presented and on each trial the participants had to manipulate either the auditory or the verbal stimulus), and one simultaneous dual task condition (in which participants

were required to perform both types of manipulation on each trial). Phase synchronization was examined for fronto-parietal and fronto-temporal electrode pairs in the theta, alpha, beta, and gamma bands for manipulation trials in comparison to the inter-trial interval. They found increased theta fronto-temporal phase synchronization for the auditory-verbal condition, simultaneous condition, and the auditory-verbal manipulations in the sequential condition. In contrast, theta fronto-parietal synchronization was increased for the visuo-spatial condition, the simultaneous condition, and the visuo-spatial manipulations of the sequential condition. Increased synchronization was not found in the other frequency bands. Thus, the authors concluded that theta synchronization is important for linking task-relevant brain regions during a working memory task, with fronto-temporal synchronization occurring in the auditory-verbal modality and fronto-parietal synchronization occurring in the visuo-spatial modality.

Finally, in the only EEG coherence study to examine working memory with the N-back task, Perfetti et al. (2014) examined group differences between individuals with high and low fluid intelligence (as measured by the Raven Advanced Progressive Matrices). In this study, participants performed verbal and spatial versions of a 3-back task. EEG coherence was examined for frontal electrode pairs for targets (match trials), lures (items that matched the stimulus presented two or four trials previously), and non-targets. They found that participants with high fluid intelligence exhibited increased theta coherence between frontal pairs for lures versus targets and non-targets, whereas individuals with low fluid intelligence exhibited decreased coherence. They also reported a significant positive correlation between frontal theta coherence and fluid intelligence. This study did not examine the effects of increasing working memory load on EEG coherence; however, the trials containing lures may be thought of as more difficult trials requiring increased executive control. However, this may not be a measure of working memory *per se*, but rather the ability to overcome interference in working memory. Unfortunately, this study did not examine coherence between frontal and posterior regions. Nevertheless, the results, which point to the importance of theta coherence in the performance of executive tasks, are consistent with the other findings reviewed above.

Thus, there is increasing evidence for the strong involvement of coherence in the theta and gamma bands in the performance of working memory tasks, an there is also evidence for a coupling between the theta and gamma bands (for reviews, see Fell & Axmacher, 2011; Klimesch, Freunberger, Sauseng, & Gruber, 2008; Sauseng, Griesmayr, Freunberger, &

Klimesch, 2010). It is hypothesized that interregional fronto-posterior theta coherence represents the coordination of brain areas required for the executive aspect of working memory with posterior modality-specific storage sub-systems and that the nesting of higher frequency oscillations into theta cycles reflects the organization of information into sequential representations (Sauseng et al., 2010).

1.8 EEG Power and Coherence in Alzheimer's Disease and Mild Cognitive Impairment

It has been well-established that AD patients demonstrate increased delta and theta power and decreased alpha and beta power while at rest (C. Babiloni et al., 2015; 2011; Başar et al., 2013; Rossini, Rossi, Babiloni, & Polich, 2007), with this pattern increasing with disease progression (Drago et al., 2011). In contrast, a major reduction in the delta frequency range during the performance of a cognitive task has been found in AD patients (Başar et al., 2013). In a cross-sectional study examining changes in power with increasing dementia severity (measured by the Clinical Dementia Rating Scale), a reduction in anterior alpha power was the earliest change noted, followed by widespread reduction of alpha power and increased posterior theta power. In the next stage, there was also a widespread reduction of beta power and theta power was increased in all regions, and in the final stage, alpha and beta powers were reduced and delta and theta powers increased in all regions (Kwak, 2006). MCI patients have been shown to exhibit a decrease in resting alpha power, which is intermediate between normal controls and AD patients and most prominent in posterior regions (C. Babiloni et al., 2011; C. Babiloni, Binetti, et al., 2006a; C. Babiloni, Visser, et al., 2010b; Moretti, Frisoni, Binetti, & Zanetti, 2011). However, increased posterior high alpha in comparison to both AD patients and controls has also been reported, along with increased posterior and frontal delta power (C. Babiloni, Binetti, et al., 2006a; C. Babiloni, Visser, et al., 2010b). Several studies have also reported no difference in power between MCI patients and controls in the delta, theta, beta, and gamma bands (e.g., C. Babiloni, Ferri, et al., 2006b; C. Babiloni et al., 2009; C. Babiloni, Visser, et al., 2010b; Huang et al., 2000). However, increased delta and theta power as well as decreased alpha and beta power in MCI patients has been related to disease progression (Drago et al., 2011; Luckhaus et al., 2008; Missonnier et al., 2006).

Many studies have examined resting synchronization in AD patients, and the most common finding from such studies (using measures of EEG or MEG coherence or synchronization) is widespread reduced alpha and beta coherence (C. Babiloni et al., 2011; 2015).

This has been found using global or average coherence measures (Besthorn et al., 1994; Jelles et al., 2008; Koenig et al., 2005; Ma, Liu, Liu, Zhou, & Zhou, 2014; Stam et al., 2005; 2002; Stam, van der Made, Pijnenburg, & Scheltens, 2003) as well as by examining specific electrode pairs, revealing decreased coherence in cross-hemisphere frontal, temporal, parietal, and occipital pairs (Adler, Brassen, & Jajcevic, 2003; C. Babiloni, Ferri, et al., 2004b; Fonseca, Tedrus, Carvas, & Machado, 2013; Fonseca, Tedrus, Prandi, Almeida, & Furlanetto, 2011; Jiang, 2005a; Kai, Asai, Sakuma, Koeda, & Nakashima, 2005; Knott, Mohr, Mahoney, & Ilivitsky, 2000; Sankari, Adeli, & Adeli, 2012; Wada, Nanbu, Koshino, Yamaguchi, & Hashimoto, 1998b) as well as decreased long distance intrahemispheric (particularly fronto-parietal) coherence (C. Babiloni, Ferri, et al., 2006b; Jiang, 2005a; Kai et al., 2005; Leuchter et al., 1992; Locatelli, Cursi, Liberati, Franceschi, & Comi, 1998; Sankari et al., 2012; Wada, Nanbu, Kikuchi, Koshino, Hashimoto, & Yamaguchi, 1998a). Locatelli et al., (1998) calculated the percentage decreased alpha coherence for local and long distance pairs in AD patients versus controls and found a substantially greater decrease for long distance pairs, supporting the view that AD as a disconnection syndrome involving predominantly long distance cortico-cortical tracts, though a widespread disturbance in coherence is clearly present. A minority of studies have reported no difference in coherence in the alpha (Jelles et al., 2008; Ma et al., 2014; Stam et al., 2003) or beta (Jiang, 2005a; Knott et al., 2000) bands in AD patients; however, variability in the electrode pairs considered and the method of calculating synchronization (e.g., global, averaged, particular pairs) may account for these findings.

Variable findings have been reported for coherence in the delta, theta, and gamma frequency bands. For example, several authors reported no difference in the lower frequency bands (Fonseca et al., 2011; 2013; Jelles et al., 2008; Leuchter et al., 1992; Ma et al., 2014; Stam et al., 2002; 2003; 2005), whereas others have reported decreased coherence in both interhemispheric and long distance intrahemispheric pairs (Adler et al., 2003; C. Babiloni, Ferri, et al., 2004b; 2006b; Jiang, 2005a; Knott et al., 2000; Sankari et al., 2012; Wada, Nanbu, Kikuchi, Koshino, Hashimoto, & Yamaguchi, 1998a; Wada, Nanbu, Koshino, Yamaguchi, & Hashimoto, 1998b). In rare cases, increased coherence has been reported in AD patients in the lower frequency bands, for example higher global delta coherence in moderate to severe AD patients in comparison to controls (Koenig et al., 2005) and higher interhemispheric temporal theta coherence (Kai et al., 2005). Fewer studies have examined the gamma band, and results

have been variable here as well. For example, several studies found no difference in AD patients (C. Babiloni, Ferri, et al., 2004b; Jelles et al., 2008; Koenig et al., 2005; Ma et al., 2014; Stam et al., 2005), and others have reported decreased average coherence (Stam et al., 2002) and decreased fronto-temporal, fronto-central, fronto-parietal, and parieto-occipital coherence (C. Babiloni, Ferri, et al., 2006b; Tao & Tian, 2005).

Studies of spontaneous (i.e., resting) coherence in MCI patients have produced variable results; however, the picture is clarified when the particular regions considered are taken into account. Specifically, when a global or averaged coherence or synchronization measure is used, there has been no report of differences between MCI patients and controls in the delta, theta, and alpha bands (Gómez, Stam, Hornero, Fernández, & Maestú, 2009; Koenig et al., 2005; Stam et al., 2003), while decreased coherence has been reported for the beta (Gómez et al., 2009; Koenig et al., 2005) and gamma bands (Gómez et al., 2009). A decrease in coherence between frontal and posterior regions has been a relatively consistent finding across frequency bands (C. Babiloni, Ferri, et al., 2006b; Moretti et al., 2008; Tóth et al., 2014; Xu et al., 2014; however, see Tao & Tian, 2005). Typically, no difference between MCI patients and controls is reported for interhemispheric frontal, temporal, and parietal electrode pairs as well as for local intrahemispheric pairs (C. Babiloni, Ferri, et al., 2006b; Jiang, Zheng, & Yu, 2008; Moretti et al., 2008; Tao & Tian, 2005; Teipel et al., 2009). However, decreased interhemispheric coherence has been reported for frontal pairs in the delta (C. Babiloni, Ferri, et al., 2006b; Tóth et al., 2014) and theta bands (C. Babiloni, Ferri, et al., 2006b) and for temporal and parietal pairs in the alpha band (Teipel et al., 2009), and conversely, one study reported increased interhemispheric coherence frontal pairs in the delta band and for temporal pairs in the delta, theta, and alpha bands (Moretti et al., 2008). Overall, the current research suggests that coherence changes in MCI patients may not be easily detectable using global or average measures, and that a disturbance of fronto-posterior connectivity may be an early sign of AD, whereas interhemispheric connections are relatively preserved at this early stage.

Relatively few studies have examined event-related coherence in AD and MCI patients. Event-related coherence is the measure of coherence during the performance of a cognitive task and is reflective of the activity of sensory and cognitive networks (Başar et al., 2013). Thus, it is highly relevant to understanding the functional neural mechanisms underlying executive dysfunction in MCI and AD. In AD patients, EEG coherence has been examined during the

performance of visual oddball tasks (Başar, Güntekin, Tülay, & Yener, 2010; Güntekin, Saatçi, & Yener, 2008), short-term memory tasks (Hogan, Swanwick, Kaiser, Rowan, & Lawlor, 2003; Pijnenburg et al., 2004), and target counting (Tao & Tian, 2005); however, no studies to date have examined EEG coherence in AD patients during the performance of a task of executive functioning. Event-related coherence has been reported to be increased overall during the performance of a cognitive task in comparison to the control condition (Başar et al., 2010); however, in one study with increasing short-term memory loads, coherence was not affected by load (Hogan et al., 2003). Furthermore, decreased coherence was more widespread in AD patients during task performance than during control tasks (Başar et al., 2010; Tao & Tian, 2005). During a visual oddball task, fronto-posterior coherence has been shown to be reduced in AD patients in delta, theta, and alpha bands, whereas interhemispheric coherence was unaffected (Başar et al., 2010; Güntekin et al., 2008). In contrast, during short-term memory tasks, coherence was reported to be decreased in alpha and beta bands, while the lower frequency bands were not affected (Hogan et al., 2003; Pijnenburg et al., 2004).

In MCI patients, event-related coherence has been examined during short-term memory tasks (Bajo et al., 2010; Pijnenburg et al., 2004), target counting (Tao & Tian, 2005), and in one set of studies, a working memory (mental addition) task (Jiang, 2005b; Jiang et al., 2008; L.-L. Zheng, Jiang, & Yu, 2007). In one study that examined intrahemispheric coherence in the gamma band during a target detection task, no differences were observed between MCI patients and controls at rest; however, MCI patients exhibited reduced fronto-temporal and fronto-central coherence during task performance (fronto-parietal coherence was not examined) (Tao & Tian, 2005). Two studies have examined synchronization likelihood during the performance of short-term memory tasks: one used EEG during maintenance of visual stimuli (Pijnenburg et al., 2004) and one used MEG during a modified Sternberg task in which a set of 5 target letters were encoded and participants were then presented with a series of letters and required to indicate with a button press each time a target was detected (Bajo et al., 2010). Pijnenburg et al. reported increased overall synchronization in the alpha band in MCI patients in comparison to controls with subjective memory complaints, both during the resting and short-term memory conditions (no differences were reported for delta, theta, beta, and gamma). Bajo et al. reported increased interhemispheric anterior synchronization and decreased intrahemispheric synchronization in temporal and central regions in the alpha and beta bands as well as increased anterior and

posterior synchronization and decreased synchronization in intrahemispheric temporal, central, central-posterior, and fronto-posterior regions in the gamma band during the modified Sternberg task (the delta and theta bands were not examined in this study).

Finally, in a series of studies examining EEG coherence during the performance of a mental addition task with three levels (Jiang, 2005b; Jiang et al., 2008; L.-L. Zheng et al., 2007), EEG coherence was found to be affected by working memory load. Specifically, participants were required to add two numbers either once (WM1), twice (WM2), or three times (WM3), and each of these conditions were compared to the resting condition. In comparison to the resting condition, coherence was found to be lower in the WM1 condition and higher in the WM3 condition across all frequency bands and for all electrode pairs (frequency bands: delta to beta; electrode pairs: interhemispheric frontal, central, parietal, temporal, occipital and intrahemispheric fronto-central, centro-parietal, parieto-occipital, temporo-central, and temporo-parietal; no difference between rest and WM2). Furthermore, while there were no differences between MCI patients and controls during the resting condition, MCI patients exhibited widespread increased coherence across all frequency bands during the working memory task.

Thus, the existing research suggests that MCI patients exhibit a decrease in fronto-posterior coherence and no change in interhemispheric coherence while at rest; whereas a widespread increase in both interhemispheric and long distance intrahemispheric coherence is present during task performance (though decreased fronto-posterior gamma coherence has also been reported during task performance). It is hypothesized that the increased coherence during task performance may represent a compensatory mechanism in which MCI patients must recruit additional neural resources when performing cognitive functions, possibly in order to compensate for inefficient antero-posterior connections (Bajo et al., 2010; Jiang et al., 2008).

1.8.1 Relationship with cognition. In general, spectral power has been shown to be negatively correlated with cognition in the delta and theta bands and positively correlated with cognition in the alpha and beta bands. For example, negative correlations have been reported with posterior delta and anterior theta, whereas positive correlations have been reported with posterior alpha and beta (C. Babiloni et al., 2011; Garn et al., 2014; Kwak, 2006; Luckhaus et al., 2008). A similar pattern has been reported with other measures of cognitive functioning, such as visuospatial memory span (negative correlation with posterior delta), digit span (positive correlation with posterior alpha), and processing speed and executive function (positive

correlation with posterior alpha and negative correlation with frontal delta) (C. Babiloni et al., 2007; C. Babiloni, Visser, et al., 2010b). Measures of EEG coherence and synchronization, on the other hand, have shown a less consistent relationship with cognition. For example, several authors have reported no relationship between EEG coherence and MMSE scores (Adler et al., 2003; Jiang, 2005b; Leuchter et al., 1992; Stam et al., 2002), while others have reported a positive correlation between MMSE scores and fronto-parietal delta and alpha coherence and interhemispheric frontal alpha coherence (C. Babiloni, Ferri, et al., 2006b; Knott et al., 2000) and a negative correlation with intrahemispheric delta and theta coherence (Fonseca et al., 2011; Knott et al., 2000). In addition, global alpha and beta coherence has been reported to be positively correlated with scores on the Montreal Cognitive Assessment (Ma et al., 2014). EEG coherence has also been related to disease severity, with negative correlations between alpha and beta coherence and Clinical Dementia Rating (CDR) scores (C.-C. Chen, Hsu, Chiu, Hu, & Lee, 2013a; Ma et al., 2014; Ranasinghe et al., 2014). Furthermore, lower connectivity in frontal regions in the alpha band and higher intrahemispheric delta and theta coherence have been associated with poorer performance on tests of episodic memory and executive function (Fonseca et al., 2011; Ranasinghe et al., 2014). In one study that examined EEG synchronization during performance of a short-term memory task, task performance was negatively correlated with delta synchronization and positively correlated with alpha synchronization (Pijnenburg et al., 2004).

1.8.2 Relationship with neuropathology. Higher theta power and lower alpha power has been related with decreased regional cerebral blood volume in patients with AD (Mattia et al., 2003). In addition, higher posterior delta and theta power and lower posterior alpha power has been associated with hippocampal atrophy (C. Babiloni et al., 2009; Rossini et al., 2007), and higher frontal delta power has been associated with lower frontal white matter volume (C. Babiloni, Frisoni, et al., 2006c) in MCI and AD patients. Decreased alpha coherence has been related to impaired cholinergic functioning (C. Babiloni, Frisoni, et al., 2010a), and positive correlations have also been reported between posterior alpha and beta coherence and posterior white matter tract integrity as well as between anterior delta, theta, and alpha coherence and anterior white matter tract integrity (Pogarell et al., 2005; Teipel et al., 2009).

In a study conducted by Moretti et al. (2008), MCI patients were divided into groups based on the highest degree of subcortical vascular damage, cholinergic pathways vascular

damage, and hippocampal atrophy. They found that these subgroups exhibited different patterns of EEG coherence changes, with hippocampal atrophy being related to increased interhemispheric coherence (frontal and temporal in the lower frequency bands) and decreased fronto-parietal coherence in all bands. However, the changes in coherence were not proportional to the degree of hippocampal damage. In contrast, MCI patients with subcortical vascular damage exhibited a decrease in interhemispheric coherence in all bands and the largest decrease in intrahemispheric coherence (particularly in the fronto-parietal pairs), which was proportional to the amount of vascular damage. Patients with high cholinergic damage exhibited a similar pattern of decreased interhemispheric coherence, but less of a decrease in intrahemispheric coherence in comparison to patients with high subcortical vascular damage.

1.9 Overview of the Project

In summary, deficits in executive functioning are increasingly being recognized as an important aspect of very early AD and MCI. However, the neural underpinnings of this deficit remain unclear. It is now widely believed that AD is a disconnection syndrome (Bokde et al., 2009; Delbeuck et al., 2003; D. P. Salmon & Bondi, 2009), and decreased connectivity between anterior and posterior regions may account for executive dysfunction in MCI and AD. EEG coherence is a measure of functional connectivity that has been studied extensively during a resting state in AD and MCI patients (C. Babiloni et al., 2011; 2015); however, few studies have examined EEG coherence in these groups while performing a cognitive task, and only one study has done so using a task (mental addition) that taps in to executive abilities.

The primary objective of this project was to elucidate the neural substrates of executive dysfunction in MCI and AD using EEG coherence as a measure of functional connectivity. A secondary aim was to explore the relationship between EEG coherence and measures of neuropathology that have not previously been related to coherence measures. The first manuscript focuses on spontaneous EEG coherence in MCI and AD patients, and the relationships between coherence and cognition as well as measures of neuropathology are explored. Specifically, we examine how resting coherence is correlated with selected neuropsychological tests as well as measures of amyloid deposition (PiB retention) and cortical thickness, two aspects of the neuropathology of AD and MCI that have not previously been examined in relation to EEG coherence. In the second and third manuscripts, the aim was to measure EEG coherence during the performance of two well-established measures of executive

function, namely a Go/No-go inhibitory control task and an N-back working memory task. In addition, the relationships between coherence measures obtained during the performance of the executive tasks and cognitive functioning, PiB retention, and cortical thickness between are explored. This dissertation concludes with a general discussion integrating the findings across the three studies.

CHAPTER 2: STUDY 1

The Relationship Between EEG Coherence, Cognition, and Neuropathology in Mild Cognitive Impairment and Alzheimer's Disease

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2.1 Abstract

Objective: We examined the relationship between resting functional connectivity and cognitive performance and brain integrity (cortical thickness and PiB retention) in patients with mild cognitive impairment (MCI), Alzheimer's disease (AD), and normal elderly controls (NECs). *Methods:* 21 MCI patients, 16 AD patients, and 26 NECs underwent neuropsychological and EEG testing, and a subset of participants also completed MRI and PiB-PET scans. EEG coherence was calculated for a selection of electrode pairs within a fronto-parietal network for the delta, theta, alpha, beta, and gamma bands. *Results:* Reduced cortical thickness in the parahippocampal gyrus and elevated PiB retention in frontal regions was observed in both patient groups, and AD patients additionally showed reduced thickness of the anterior cingulate cortex and elevated PiB retention in parietal regions. EEG coherence was reduced for cross-hemisphere parietal regions in the delta and theta bands for AD patients only. Intrahemispheric fronto-parietal coherence was not affected in MCI patients or AD patients; however MCI patients who converted to dementia showed higher baseline fronto-parietal gamma coherence compared to MCI patients who remained stable. EEG coherence was reliably associated with PiB retention, but not cortical thickness in MCI patients and NECs. In contrast, EEG coherence was strongly related to neuropsychological test performance in AD patients, but not MCI patients or NECs. *Conclusion:* AD patients, but not MCI patients, show reduced functional connectivity between cross-hemisphere parietal regions while at rest. The relationship between EEG coherence and measures of cognition and brain integrity is variable between groups, with some evidence for a potential compensatory mechanism for higher fronto-parietal coherence in NECs.

Keywords: Alzheimer's disease (AD), mild cognitive impairment (MCI), electroencephalography (EEG), EEG coherence, cognition, PiB, cortical thickness

2.2 Introduction

Alzheimer's disease (AD) is the most common form of dementia and is a major health concern worldwide (Canadian Study of Health and Aging Working Group, 1994; World Health Organization, 2012). Though our understanding of the neuropathology of AD has advanced greatly over the past 100 years, there is still much to learn about how the disease impacts brain functioning and the relationship between brain functioning and cognitive functioning. AD is increasingly being viewed as a syndrome of disconnection between brain areas (e.g., Bokde et al., 2009; De Lacoste & White, 1993; Delbeuck et al., 2003); however, the relationship between such functional disconnection and measures of cognition and neuropathology is still poorly understood.

AD is a progressive neurodegenerative disorder involving complex neuropathological changes. Prominent episodic memory impairment is typically seen as the main feature of the clinical presentation; however, impairment in at least one other cognitive domain must also be present for a diagnosis of probable AD to be made (McKhann et al., 2011). Mild cognitive impairment (MCI) is an important concept in the study of AD, as it may represent a transitional stage between normal aging and AD (Petersen et al., 1999; 2014) and therefore represents a group of individuals who may offer insights into early diagnosis and the effects of early treatment interventions. The revised National Institute on Aging-Alzheimer's Association (NIA-AA) diagnostic criteria (Albert et al., 2011) define MCI as the presence of a reported cognitive complaint (by self or informant), objective cognitive impairment, preserved functional abilities, and a failure to meet diagnostic criteria for dementia. MCI patients can be classified as either amnestic (aMCI) or non-amnestic (naMCI), in either a single domain or multiple domains of cognitive function. The current consensus is that most MCI patients who go on to develop AD most commonly exhibit an impairment in episodic memory, although other cognitive domains may also be impaired (Albert et al., 2011).

Two of the pathological hallmarks of AD are amyloid-β (Aβ) plaques and neurofibrillary tangles (NFTs). With the recent development of amyloid imaging techniques using positron emission tomography (PET), it has become possible to examine the pattern of amyloid deposition in vivo. The most well-known radiotracer used in this technique Pittsburgh Compound-B (PiB), which binds to cortical areas containing amyloid deposits (Klunk et al., 2004). PiB retention has been found to be elevated in AD patients in comparison to normal

controls, particularly in the middle frontal and prefrontal cortex, parietotemporal cortex, posterior cingulate cortex, precuneus, occipital lobes, thalamus, and striatum (Berti et al., 2010; Masdeu et al., 2012). There are several other neuropathological features of AD, including neuronal cell loss, synaptic loss, white matter loss, glial cell reactions, neuropil threads, and amyloid angiopathy, and neurochemical changes (DeKosky, 2001; Lage, 2006; Perl, 2010; Suhara, Higuchi, & Miyoshi, 2008; Thompson et al., 2007). Cortical thinning is evident in the entorhinal cortex in the early phases of the illness (Román & Pascual, 2012) and, in the late stages, many brain areas are affected by cortical thinning (Lerch et al., 2005).

The neuropathological features of aMCI are typically intermediate between normal aging and very early AD, including the presence of neurofibrillary tangles in the medial temporal lobes, diffuse cortical amyloid deposition, synaptic loss, and degeneration of the cholinergic system (Drago et al., 2011; Mufson et al., 2012; Petersen et al., 2006; Stephan et al., 2012). However, there is considerable heterogeneity in the presence of the gross neuropathological features of AD, with many MCI patients not showing significant neuropathological changes (Mufson et al., 2012; Stephan et al., 2012). Nevertheless, hypometabolism has been reported in the medial temporal lobes, parietotemporal cortex, and posterior cingulate cortex in aMCI, and metabolic impairment in these regions is predictive of conversion to AD (Berti et al., 2010; Petersen et al., 2014). PiB retention with a similar distribution as seen in AD has been reported in approximately 50% of amnestic MCI patients, and those who convert to AD have greater baseline PiB retention than those who do not convert (Berti et al., 2010).

It is hypothesized that AD is a syndrome of disconnection between brain areas in which the neuropathology of AD may result in the failure of the brain to integrate the processing of various regions into effective networks, which may in turn underlie changes in cognitive functioning (Bokde et al., 2009; Delbeuck et al., 2003; D. P. Salmon & Bondi, 2009). Resting-state functional magnetic resonance imaging (fMRI) studies have found decreased connectivity in the default mode network (DMN) in AD patients (Balachandar et al., 2014; Beason-Held, 2011; Bokde et al., 2009; Hafkemeijer et al., 2012; Pievani et al., 2011; for a review, see Filippi & Agosta, 2011). However, some studies also reported increased connectivity within the frontal, parietal, and occipital lobes, between the posterior cingulate cortex and frontal/parietal regions, and between the hippocampus and prefrontal cortex, which has been interpreted as evidence for a compensatory-recruitment hypothesis (Filippi & Agosta, 2011; Hafkemeijer et al., 2012).

Altered connectivity has also been reported in other functional networks examined with fMRI, including the dorsal attention network, fronto-parietal central executive network, salience network (most prominently involving the dorsal anterior cingulate and orbital frontoinsula), and sensory-motor network (Brier et al., 2012). For example, decreased functional connectivity has been observed in the fronto-parietal network (Agosta et al., 2012; Dhanjal & Wise, 2014; K. Wang et al., 2007; Z. Wang et al., 2013), whereas increased connectivity has been reported in the frontal and salience networks (Agosta et al., 2012; Balachandar et al., 2014; K. Wang et al., 2007; L. Wang et al., 2006; H.-Y. Zhang et al., 2009; J. Zhou et al., 2010; however see Dhanjal & Wise, 2014 for decreased connectivity in the salience network). Studies of global brain functional connectivity have reported a general pattern of decreased anterior-posterior connectivity and greater connectivity within lobes (Filippi & Agosta, 2011).

In MCI patients, decreased functional connectivity in the DMN is also reported, though to a lesser degree than that seen in AD. In addition, MCI who convert to dementia show greater disconnection than non-converters (Beason-Held, 2011; Filippi & Agosta, 2011; Hafkemeijer et al., 2012; Pievani et al., 2011; Sheline & Raichle, 2013; Teipel et al., 2013). In other functional networks, the findings have been somewhat mixed for MCI patients. While increased connectivity within frontal regions has been reported (Bai et al., 2009; Liang et al., 2011; Z. Qi et al., 2010), other studies have reported reduced frontal connectivity (Sorg et al., 2007) or no difference between MCI patients and healthy controls (Agosta et al., 2012). Research on the fronto-parietal central executive network and salience network in MCI patients is limited; however, two studies have reported no difference between MCI patients and controls in salience network connectivity (Agosta et al., 2012; He et al., 2014), and one study reported no difference in fronto-parietal connectivity (Agosta et al., 2012).

In recent years, there has been increasing interest in the study of quantitative electroencephalogram (EEG) measures as an inexpensive and non-invasive method of potential early diagnosis in MCI and AD (C. Babiloni et al., 2011; 2015; Başar, 2013). While resting state fMRI studies can provide an index of functional connectivity on a timescale of seconds, EEG and magnetoencephalography (MEG) studies examine synchronous oscillations on a timescale of milliseconds. EEG measures electrical brain activity or frequency oscillations at the scalp, and the relative power (magnitude) of the signal at each frequency band can be examined following the spectral decomposition of the oscillatory activity. Frequency bands commonly examined

include delta (0.5-3.5 Hz), theta (3.5-7.5 Hz), alpha (7.5-12.5 Hz), beta (7.5-30 Hz) and low gamma (30-60 Hz). EEG coherence, which represents the functional interaction between two brain regions (Nunez et al., 1997), can also be calculated for each frequency band. Specifically, EEG coherence is a linear measure of the covariance between two neuroelectrical signals over time, derived from the spectral decomposition of the EEG for a given frequency range (Roach & Mathalon, 2008). Coherence is sensitive to both magnitude and phase angle; however, it is most strongly influenced by phase (Nunez & Srinivasan, 2006; Srinivasan et al., 2007). There are also other methods of calculating synchronization between brain regions, including synchronization likelihood (a measure of both linear and non-linear relationships between the two channels), and phase coherence or synchronization (Pievani et al., 2011). Increases in synchronization between two brain regions can be interpreted as representing some commonality in the generator driving the two areas. The two regions may be driven by a common generator, one may drive the other, or they may mutually interact (Başar et al., 2013).

2.2.1 EEG Power and Coherence in Alzheimer's Disease & Mild Cognitive Impairment

Changes in amplitude across the power spectrum are commonly reported in AD patients. Specifically, increased resting state delta and theta power and decreased resting alpha and beta power are well-established findings in AD patients (C. Babiloni et al., 2011; 2015; Başar et al., 2013; Rossini et al., 2007). This pattern increases with disease progression, with the earliest changes occurring in the alpha band, followed by changes in theta, then beta, and finally delta bands (Drago et al., 2011; Kwak, 2006). A reduction in low-frequency alpha power has also been reported in MCI patients, which is of intermediate magnitude between normal controls and AD patients and most prominent in posterior regions (C. Babiloni et al., 2011; 2015; C. Babiloni, Binetti, et al., 2006a; C. Babiloni, Visser, et al., 2010b; Moretti et al., 2011). Similar to reports in AD patients, increased frontal and posterior delta power has been reported in MCI patients relative to controls, and additionally, increased high-frequency alpha in posterior regions has been found in MCI patients (C. Babiloni, Binetti, et al., 2006a; C. Babiloni, Visser, et al., 2010b). In contrast, several studies have reported no difference in power between MCI patients and controls in the delta, theta, beta, and gamma bands (C. Babiloni et al., 2009; e.g., C. Babiloni, Ferri, et al., 2006b; C. Babiloni, Visser, et al., 2010b; Huang et al., 2000). Despite the lack of group differences between MCI patients and controls in many cases, increased delta and theta

power as well as decreased alpha and beta power in MCI patients has been related to disease progression (Drago et al., 2011; Luckhaus et al., 2008; Missonnier et al., 2006).

Resting state EEG and MEG coherence or synchronization in AD has been examined in many studies, with the most common finding being reduced alpha and beta coherence (C. Babiloni et al., 2011; 2015; see Table 2.1 for a summary of studies that have examined EEG or MEG synchronization measures and reported statistical tests for AD patients in comparison to normal controls). This has been found for global synchronization measures, in which an overall averaged synchronization value is obtained for each frequency band, as well as for cross-hemisphere electrode pairs (in particular for frontal, central, and parietal pairs in the alpha band and for frontal pairs in the beta band). For long distance intrahemispheric electrode pairs, the most consistent finding is reduced alpha synchronization for fronto-parietal pairs. Findings for resting state EEG coherence in the delta, theta, and gamma frequency bands have been more variable, with some studies reporting reduced coherence in interhemispheric and/or intrahemispheric electrode pairs, and other studies reporting no differences between groups (see Table 2.1).

In contrast to the findings in the alpha band for AD patients, studies of resting state coherence in MCI patients suggest that global alpha synchronization is not affected in MCI (see Table 2.2 for a summary of studies that have examined resting state synchronization EEG or MEG synchronization in MCI patients in comparison to normal controls). However, decreased global synchronization has been reported in the beta and gamma bands in MCI patients. When specific electrode pairs are examined, inter-hemispheric coherence is typically unaffected, but fronto-parietal coherence has been reported to be reduced in MCI patients, particularly in the delta and alpha bands. Thus, coherence changes in MCI patients may not be easily detectable using global or average measures, particularly for lower frequency bands, and a disturbance of fronto-posterior connectivity may be an early sign of AD, whereas interhemispheric connections are relatively preserved at this early stage.

It is of interest to know whether measures of EEG coherence can predict conversion to dementia in MCI patients. In one study that examined fronto-parietal EEG coherence, increased baseline coherence was observed for midline fronto-parietal pairs in all frequency bands and for left fronto-parietal pairs in the alpha, beta, and gamma bands in MCI patients who converted to dementia in comparison to MCI patients who remained stable over a 14 month follow-up period

(Rossini et al., 2006). The authors interpret this somewhat paradoxical finding as a reflection of cholinergic impairment, which alters reciprocal inhibition between the delta and alpha bands and results in an unselective increase in power and coherence across frequency bands. In another study that examined temporo-parietal coherence, there was no difference in baseline coherence between MCI patients who remained stable versus those who progressed to dementia after a follow-up period of 21 months (Jelic et al., 2000).

Measures of EEG coherence and synchronization have shown an inconsistent relationship with cognition. Several authors have reported that EEG coherence is not correlated with MMSE scores (Adler et al., 2003; Jiang, 2005b; Leuchter et al., 1992; Stam et al., 2002), while others have reported a positive correlation between MMSE scores and fronto-parietal delta and alpha coherence and interhemispheric frontal alpha coherence (C. Babiloni, Ferri, et al., 2006b; Knott et al., 2000) and a negative correlation with intrahemispheric delta and theta coherence (Fonseca et al., 2011; Knott et al., 2000). In addition, global alpha and beta coherence has been reported to be positively correlated with scores on the Montreal Cognitive Assessment (Ma et al., 2014), and lower connectivity in frontal regions in the alpha band and higher intrahemispheric delta and theta coherence have been associated with poorer performance on tests of episodic memory and executive function (Fonseca et al., 2011; Ranasinghe et al., 2014). More studies addressing the relationship between resting state coherence and cognition are needed to clarify this issue; however, there is some evidence that coherence in the lower frequency bands may have a negative relationship with cognition, whereas coherence in the alpha and beta bands may have a positive relationship with cognition.

Few studies have examined the relationship between EEG coherence and neuropathology in AD and MCI patients. However, decreased alpha coherence has been related to impaired cholinergic functioning (C. Babiloni, Frisoni, et al., 2010a), and positive correlations have been reported between posterior alpha and beta coherence and posterior white matter tract integrity as well as between anterior delta, theta, and alpha coherence and anterior white matter tract integrity (Pogarell et al., 2005; Teipel et al., 2009). In one study, MCI patients with a high degree of hippocampal atrophy exhibited increased interhemispheric coherence (frontal and temporal in the lower frequency bands) and decreased fronto-parietal coherence in all bands, though the changes were not proportional to the degree of hippocampal damage. In contrast, MCI patients with subcortical vascular damage exhibited a decrease in interhemispheric

coherence in all bands and the largest decrease in intrahemispheric coherence, particularly in the fronto-parietal pairs, which was proportional to the amount of vascular damage (Moretti et al., 2008). To our knowledge, no studies to date have examined the relationship between EEG coherence and cortical thickness or PiB retention.

2.2.2 The Present Study

The primary aim of the present study was to examine the relationship between resting state EEG coherence and measures of cognition and neuropathology in AD and MCI. To this end, we collected data on neuropsychological test performance, resting spectral EEG power and coherence in selected electrode pairs, cortical thickness, and PiB retention in AD patients, MCI patients, and normal elderly controls. After a follow-up period of approximately three years, we re-examined baseline EEG coherence in the MCI patients who progressed to dementia versus those who remained stable.

We first examined group differences on each of the measures and then conducted several exploratory correlations to investigate interrelationships between these variables. Based on the previous literature, we predicted reduced spectral EEG power in the alpha band in both MCI and AD patients, as well as reduced beta power and increased delta and theta power in AD patients. With regards to resting EEG coherence, we predicted reduced coherence across frequency bands for both inter- and intra-hemispheric electrode pairs in AD patients and reduced fronto-parietal coherence in the delta and alpha bands in MCI patients, compared to controls. Based on the limited literature to date, we also predicted higher fronto-parietal coherence in MCI patients who progress to dementia versus those who remain stable. Finally, we predicted increased PiB retention in prefrontal and parietal areas as well as decreased cortical thickness in the medial temporal lobes in both AD and MCI patients.

2.3 Methods

2.3.1 Participants

Twenty-one MCI patients, 16 AD patients, and 26 normal elderly controls (NECs) were selected for inclusion in the final sample of the present study. A general health questionnaire was administered to screen participants for neurological conditions other than MCI or AD, medical conditions that might affect cognition (e.g., uncontrolled thyroid dysfunction, B_{12} deficiency, alcohol abuse), and psychiatric disorders (other than mild depression). Additionally, the Geriatric Depression Scale (GDS; Yesavage et al., 1982) was administered, and any

participant with a score greater than six was not admitted to this study. The Subjective Memory Complaints Scale (SMCS; Schmand, Jonker, Hooijer, & Lindeboom, 1996) was also administered in order to characterize self-ratings of memory functioning. From the larger sample initially recruited for this study, two MCI patients, one AD patient, and seven NECs were excluded from data analyses in order to generate a sample with identical participants to those used in the analysis of data collected during two experimental tasks (data not presented here; see Johns & Phillips, 2015a; 2015b).

MCI and AD participants were recruited and diagnosed at the Memory Clinic of the Sir Mortimer B. Davis–Jewish General Hospital (JGH), a tertiary care referral center of McGill University, Montreal. Their clinical evaluations included full medical, neuropsychological, and neuroradiological assessments. NECs were recruited from research participation databases at the Cognition, Aging, and Psychophysiology Laboratory at Concordia University and the Memory Clinic at the JGH. Written informed consent was obtained from all participants, who were compensated $10 per hour for their participation. Participants were tested at Concordia University and the Jewish General Hospital, and ethical approval for the study was obtained from both institutions involved.

2.3.1.1 MCI patients. A diagnosis of MCI was given based on agreed-upon criteria (Petersen et al., 2009; Winblad et al., 2004), which included a subjective report of cognitive decline (by either the individual or family), which was gradual and of at least 6 months duration, a documentation of objective cognitive impairment on neuropsychological testing (i.e., ±1.5 SD of age-appropriate norms), the absence of significant impairment in activities of daily living, and failure to meet the ADRDA-NINCDS criteria for dementia (McKhann et al., 1984), as determined by the assessing physician in the Memory Clinic. All MCI patients were amnestic, either demonstrating an impairment on measures of episodic memory alone or impairments in episodic memory plus other cognitive domains.

2.3.1.2 AD patients. A diagnosis of AD was given based on the ADRDA-NINCDS criteria for possible or probable AD (McKhann et al., 1984), which included an established progressive cognitive decline and the absence of any other disease capable of producing the dementia syndrome. Only participants who were deemed to be able to sign the consent form without assistance were included in this study; thus, all AD patients had a mild to moderate level of cognitive impairment and no severe cases were included (average MoCA score = 19.3).

2.3.1.3 Normal elderly controls. NECs were screened for general cognitive function using the Montreal Cognitive Assessment (MoCA; Nasreddine et al., 2005), a cognitive screening tool that is sensitive to detecting MCI. NECs were excluded if they scored below 26 on this measure.

2.3.2 Materials and Procedure

All participants completed a neuropsychological testing session and an EEG testing session, and subset of participants also completed MRI and PiB scans. In addition, MCI patients were followed at the Memory Clinic at the Jewish General Hospital through neuropsychological and medical assessments, and were further classified into two groups for the secondary analyses reported below: MCI converters (MCI-c) and stable MCI patients (MCI-s). Seven MCI patients were diagnosed with dementia within 10 months to 4.2 years following EEG testing. The remainder of the MCI patients were considered to be stable if they completed a follow-up assessment two years or more following the EEG testing and were judged to still meet diagnostic criteria for MCI at that time. Nine MCI patients were considered to be stable, with the period of follow-up ranging from 2.1 to 4.7 years (average 3.4 years). The remaining MCI patients did not have follow-up data available at the time of this analysis. After the follow-up period, baseline demographic, neuropsychological, and EEG coherence measures were re-examined for group differences between MCI-c and MCI-s.

2.3.2.1 Neuropsychological Testing. The neuropsychological test battery was administered according to standardized procedures and in a standardized order. The battery included measures of verbal abstract reasoning (Similarities subtest of the Wechsler Adult Intelligence Scale-Third Edition, WAIS-III; Wechsler, 1997), processing speed (Symbol Search subtest of the WAIS-III; Wechsler, 1997), short-term memory span (Digit Span subtest of the WAIS-III; Wechsler, 1997), confrontational naming (Boston Naming Test, 15-item version; Kaplan, Goodglass, & Weintraub, 1983), verbal episodic memory (California Verbal Learning Test – Second Edition; Delis, Kramer, Kaplan, & Ober, 2000), working memory (Letter Number Sequencing subtest of the WAIS-III; Wechsler, 1997), phonemic and semantic verbal fluency (letters F, A, and S, and animals; Strauss et al., 2006), cognitive flexibility (Trail Making Test; Reitan, 1979; Strauss et al., 2006), and inhibitory control (Hayling Sentence Completion Test; Burgess & Shallice, 1997; and Victoria verion of the Stroop Test; Strauss et al., 2006).

2.3.2.2 EEG Recording. EEG was recorded while at rest (eyes-closed) for three minutes, as well as during three other executive function tasks, which are not presented here. During the resting condition, participants were instructed to sit comfortably with their eyes closed, and to avoid moving their heads and eyes. The data were acquired using Neuroscan Acquire software (Neuroscan, 2003) from 32 Ag/AgCl electrodes mounted in an elastic Easycap and placed according to the International 10-20 system, with a bandpass of DC-100 Hz and a sampling rate of 500 Hz. All sites were referenced to the left ear and re-referenced offline to linked ears. Electrode impedances were kept below 8 kΩ (and in most cases, below 5 kΩ). Electro-oculogram (EOG) activity was recorded supra-orbitally and from the outer canthi of both eyes in order to monitor eye movement, and corrected offline using ocular correction independent component analysis in BrainVision Analyzer 2.0 (*BrainVision Analyzer User Manual*, 2013).

2.3.2.3 Spectral analysis of EEG data. EEG data were processed offline using BrainVision Analyzer 2.0 software (*BrainVision Analyzer User Manual*, 2013). A DC drift correction and a 1-50 Hz phase shift-free Butterworth filter with a 12 db roll-off was applied to the continuous EEG files. Resting EEG was segmented in continuous 1024 ms epochs (minimum 109 epochs, $M = 193$), and segments containing deflections of greater than ±100 μV were excluded from further analysis. Data were transformed to the frequency domain using a fast Fourier transform (FFT) with a Hanning window. Average power and coherence were calculated for the following frequency bands: delta (1-3.5 Hz), theta (3.5-7.5 Hz), alpha (7.5-12.5 Hz), beta (12.5-30 Hz), and gamma (30-45 Hz).

2.3.2.4 Spectral Coherence Analysis. EEG coherence was calculated using the following formula for segment number i, fixed frequency f, and fixed channel c:

$$Coh(c_1, c_2)(f) = | CS(c_1, c_2)(f) |^2 / (| CS(c_1, c_1)(f) | | CS(c_2, c_2)(f) |),$$

where $CS(c_1, c_2)(f) = \Sigma\, c_{1,\,i}\,(f)\, c_{2,\,i}\,(f)$

The numerator contains the cross-spectrum of two EEG signals c_1 and c_2 ($CS(c_1, c_2)$) for a given frequency bin (f) and the denominator contains the autospectra for c_1 ($CS(c_1, c_1)$) and c_2 ($CS(c_2, c_2)$). The coherence value is equivalent to the squared complex correlation coefficient (Pfurtscheller & Andrew, 1999; Rappelsberger & Petsche, 1988), and coherence values range from 0 (no coherence) to 1 (maximal coherence). EEG coherence was computed for the following electrode pairs of interest: F3-F4, P3-P4, O1-O2, F3-P3, and F3-O1. These electrode pairs were chosen based on previous research that has implicated fronto-parietal network

dysfunction in MCI and AD, and the cross-hemisphere occipital pair and fronto-occipital pair were chosen for comparison to electrode pairs outside the fronto-parietal network. A Fisher's Z transformation was applied to the square root of coherence values in order to normalize the distribution for statistical analysis.

2.3.2.5 MRI acquisition and cortical thickness processing. Cortical thickness data were available for seven NECs, 17 MCI patients, and seven AD patients. MRI scans were acquired on a 1.5 Tesla Siemens Sonata Vision scanner at the Montreal Neurological Institute (MNI) and were done within one year of the EEG testing for MCI patients (M = 0.56 years) and within two years of EEG testing for NECs (M = 1.10 years) and AD patients (M = 1.21 years). High-resolution T1-weighted anatomical scans were obtained using a three-dimensional spoiled gradient echo sequence (T_R= 22ms; T_E= 9.2ms; flip angle= 30°; FOV = 256 x 256; 160 or 176 slices; 1-mm isotropic) along the sagittal plane.

MRI scans were processed using the automated CIVET pipeline (The McConnell Brain Imaging Centre, Montreal Neurological Institute). Briefly, tissue classification generated a gray and white matter surface for each subject, which was then aligned to a model surface. The difference in distance between the aligned gray and white matter surfaces was computed at each of 81924 vertices (40962 per hemisphere) using the *t-link* method, providing a measure (in mm) of cortical thickness at each of those vertices. Finally, thickness values were smoothed using a 20-mm surface smoothing filter. In order to permit analysis by region of interest (ROI), customized Automated Anatomical Labeling atlas (Tzourio-Mazoyer et al., 2002) labels were strongly warped (non-linearly) onto the subject's surface, yielding an individually-labeled surface with one label at each vertex. Next, the thickness vector file was matched against the newly created labels vector file, allowing for the computation of cortical thickness values for each ROI. The ROIs analyzed in the present study were chosen to sample frontal and parietal areas as a comparison for the EEG data as well as medial temporal areas, which are known to be affected in early AD. The five ROIs selected were the superior frontal gyrus, middle frontal gyrus, anterior cingulate cortex, superior parietal lobule, and parahippocampal gyrus (all in the left hemisphere).

2.3.2.6 PiB-PET acquisition and processing. PiB-PET data were available for 10 NECs, 13 MCI patients, and seven AD patients. Scans were acquired on a Siemens/CTI ECAT HR+ scanner in 3-dimensional imaging mode (63 parallel planes) at the MNI. All scans were done

within one year of the EEG testing for MCI patients (M = 0.57 years) and within two years of EEG testing for NECs (M = 0.87 years) and AD patients (M = 1.08 years). Subjects were scanned either for either 90 minutes immediately following injection of the [C-11]PiB bolus (34 frames collected) or for 40 minutes commencing 50 minutes after the injection (7 frames collected). The difference in scanning times was due to a need to shorten scan times after receiving feedback from participants that the scan time was too long.

The PiB volume was aligned to the participants' native anatomy according to the T1-weighted MRI scan. This was followed by registration of both native-space volumes to the MNI symmetrical template using a 12-parameter linear transformation. The resulting stereotactic-space dynamic volume was blurred with a 6-mmm full-width at half-maximum Gaussian filter in order to minimize the effects of random high-frequency spikes in the data and increase the signal-to-noise ratio. Blurring filter width was minimized in order to prevent the blurring of the signal within the cerebellar gray and white matter.

Ratio values were computed at each voxel using all seven frames collected during 40 minute scans and the last five frames collected during 90 minute scans (50 minutes post-injection, 40 minutes total scan time). First, the area under the curve (AUC) across time was computed for the cerebellar gray matter reference values, and at each voxel within the volume. Ratios were then computed by dividing each voxel's AUC value by the cerebellar gray AUC. Average PiB ratio values were computed for each ROI as defined by the Automated Anatomical Labeling atlas (Tzourio-Mazoyer et al., 2002). Consistent with the cortical region ROIs, the six ROIs that were analyzed in the present study were the superior frontal gyrus, middle frontal gyrus, anterior cingulate cortex, superior parietal lobule, hippocampus, and parahippocampal gyrus (all in the left hemisphere).

2.4 Results

2.4.1 Participant Characteristics

As can be seen in Table 2.3, there were no significant differences between groups in age, educational level, and sex distribution. Participants were also comparable on level of depressive symptomatology, as measured by the Geriatric Depression Scale. As expected, the groups differed significantly in their report of subjective memory complaints, $F(2, 60) = 5.56$, $p = .006$, $\eta^2_p = .16$, with AD patients scoring higher on the SMCS than NECs, ($p = .001$), and a trend for MCI patients scoring higher than NECs ($p = .069$). The groups also differed significantly on the

MoCA test, $F(2, 60) = 31.60$, $p < .001$, $\eta^2_p = .51$, with AD patients performing worse than MCI patients ($p = .007$), and MCI patients in turn performing worse than NECs ($p < .001$).

2.4.2 Statistical Analysis

Statistical analysis was conducted using SPSS v.22.0 software. For analyses with more than one degree of freedom in the numerator, a Huynh and Feldt (1976) correction was used for violations of sphericity. In these cases, the unadjusted degrees of freedom, the adjusted *p*-value, and the Huynh-Feldt epsilon value (ε) are reported.

2.4.3 Neuropsychological Testing

The results for the neuropsychological testing are presented in Table 2.4, including group means and standard deviations as well as a summary of group differences. Each neuropsychological test was analyzed with a separate univariate or multivariate analysis of variance (ANOVA), as appropriate. Neuropsychological test scores revealed that AD patients performed significantly worse than controls on a number of measures across several cognitive domains. These included verbal abstract reasoning (Similarities subtest, $p < .001$), visual processing speed (Symbol Search, $p < .001$), Digit Span forward ($p = .002$), confrontational naming (Boston Naming Test, $p < .001$), verbal episodic memory (CVLT, $p < .001$ for total learning trials and delayed recall), working memory (Letter-Number Sequencing subtest, $p = .002$), verbal fluency (semantic, $p < .001$ and phonemic, $p = .003$), and inhibitory control (errors on the Stroop test, $p = .009$ and errors on the Hayling test, $p = .001$). MCI patients also performed significantly worse than controls on a number of measures, including verbal abstract reasoning (Similarities subtest, $p = .001$), visual processing speed (Symbol Search, $p = .009$), verbal episodic memory (CVLT, $p < .001$ for total learning trials and delayed recall), semantic verbal fluency ($p < .001$), and inhibitory control (Hayling test errors, $p = .013$).

2.4.4 Spectral EEG Power Analysis

Average power for each frequency band was measured for frontal (F3, Fz, F4), central (C3, Cz, C4), parietal (P3, Pz, P4), and occipital (O1, O2) electrode sites. The data were positively skewed; therefore, a logarithmic transformation was applied in order to normalize the distributions.

Mean power during the eyes-closed baseline condition for NECs, MCI patients, and AD patients is presented in Figure 2.1. The data were analyzed with a 5 x 4 x 3 mixed design ANOVA, where the effects of frequency band (delta, theta, alpha, beta, gamma), electrode site

(frontal, central, parietal, occipital), and group (NEC, MCI, AD) were examined. There was no main effect of group, $F(1, 61) = 1.48$, $p = .236$, $\eta^2_p = .05$. There was a main effect of frequency band, $F(4, 240) = 491.54$, $p < .001$, $\eta^2_p = 0.89$, $\varepsilon = .683$, such that power was greatest in the alpha band followed by delta, theta, beta, and gamma ($p < .01$ in all cases). The interaction between group and frequency band was not significant; however, there was a significant frequency band x electrode site x group interaction, $F(24, 720) = 2.31$, $p = .028$, $\eta^2_p = 0.071$, $\varepsilon = .320$. Pairwise comparisons revealed that MCI patients had reduced beta power in comparison to NECs at the central electrodes ($p = .043$) and both MCI and AD patients had reduced beta power at parietal ($p = .048$ and $p = .029$, respectively) and occipital electrodes ($p = .037$ and $p = .012$, respectively). In addition, AD patients had greater gamma power than MCI patients at the central electrodes ($p = .028$). The group differences at the posterior sites in the alpha band failed to reach statistical significance due to large variability in the data (parietal: NEC vs. MCI, $p = .355$ and NEC vs. AD, $p = .424$; occipital: NEC vs. MCI, $p = .350$ and NEC vs. AD, $p = .314$).

2.4.5 EEG Coherence

The overall effect of frequency band was examined by entering all variables into a 5 x 5 x 3 mixed design ANOVA. The within subjects factors were frequency band (delta, theta, alpha, beta, gamma) and electrode pair (F3-F4, P3-P4, O1-O2, F3-P3, F3-O1). The between subjects factor was group (NEC, MCI, AD). There was a main effect of frequency band, $F(4, 240) = 31.78$, $p < .001$, $\eta^2_p = 0.35$, $\varepsilon = .617$, such that coherence was highest in the delta band ($M = .487$, $SE = .015$) followed by alpha ($M = .422$, $SE = .012$, $p < .001$ vs. delta) and theta ($M = .417$, $SE = .011$, $p < .001$ vs. delta), which were higher than gamma ($M = .379$, $SE = .013$; $p = .013$ vs. alpha, $p = .022$ vs. theta). Coherence was lowest for the beta band ($M = .339$, $SE = .010$, $p < .001$ vs. gamma).

The effects of electrode pair and group were examined separately for each frequency band and family of electrode pairs. The family of cross-hemisphere homologous pairs was analyzed using 3 x 3 mixed design ANOVAs to examine the effects of electrode pair (F3-F4, P3-P4, O1-O2) and group (NEC, MCI, AD), and the family of long distance intra-hemispheric pairs was analyzed using 2 x 3 mixed design ANOVAs to examine the effects of electrode pair (F3-P3, F3-O1) and group (NEC, MCI, AD). The data for all electrode pairs are presented in Figure 2.2.

2.4.5.1 Cross-hemisphere homologous pairs. The ANOVA results for cross-hemisphere homologous pairs are presented in Table 2.5 and the means are illustrated in Figure

2.2. There was a main effect of electrode pair for each of the five frequency bands in which coherence was highest for O1-O2, followed by P3-P4, and then F3-F4 ($p < .001$ in all cases).

There was also a main effect of group in the delta band, and pairwise comparisons revealed that coherence was significantly lower for AD patients in comparison to both MCI patients and normal controls ($p < .05$). There were also non-significant trends for main effects of group in the theta and alpha bands. Pairwise comparisons revealed that coherence was lower in AD patients in comparison to MCI patients in the theta and alpha bands ($p < .05$), and that there was a trend for lower coherence in AD patients in comparison to NECs in the theta band ($p < .10$).

Though the group x electrode pair interactions were not significant, planned pairwise comparisons for these frequency bands revealed that AD patients had lower coherence than both NECs and MCI patients for only P3-P4 and O1-O2 in the delta band and for only P3-P4 in the theta band ($p < .05$ in all cases). In the alpha band, coherence was lower in AD patients in comparison to MCI patients for F3-F4 and P3-P4 ($p < .05$). Overall, these results indicate that coherence is reduced in AD primarily in the cross-hemisphere parietal pair in the lower frequency bands.

2.4.5.2 Long distance intrahemispheric pairs. The ANOVA results for long distance intrahemispheric pairs are presented in Table 2.6 and the means are illustrated in Figure 2.2. There was a main effect of electrode pair for each of the five frequency bands in which coherence was higher for F3-P3 than for F3-O1 ($p < .001$ in all cases). There were no group differences and no group x electrode pair interactions. This indicates that resting fronto-parietal coherence is higher than fronto-occipital coherence and that long distance intrahemispheric coherence while at rest is not affected in MCI and AD.

2.4.6 Cortical Thickness

Figure 2.3 shows the mean cortical thickness values for the five ROIs, which were analyzed with a multivariate ANOVA. The omnibus test was significant, $\lambda(10, 48) = .386$, $p = .006$, $\eta^2_p = 0.38$, and follow-up comparisons revealed a significant group difference for the parahippocampal gyrus, $F(2, 28) = 13.26$, $p < .001$, $\eta^2_p = 0.49$, in which MCI patients had reduced thickness in comparison to controls ($p = .027$), and AD patients had reduced thickness in comparison to both controls ($p < .001$) and MCI patients ($p = .001$). There was also a non-significant trend for a group difference for the anterior cingulate cortex, $F(2, 28) = 2.74$, $p = .082$,

$\eta^2_p = 0.16$, for which follow-up comparisons revealed significantly reduced thickness for AD patients in comparison to controls ($p = .036$), and a non-significant trend for reduced thickness in MCI patients in comparison to controls ($p = .062$). There were no significant group differences for the superior frontal gyrus, middle frontal gyrus, or superior parietal lobule.

2.4.7 PiB Retention

Figure 2.4 show the mean PiB retention values for the six ROIs, which were analyzed with a multivariate ANOVA. The omnibus test just missed the conventional cutoff for statistical significance, $\lambda(12, 44) = .426$, $p = .054$, $\eta^2_p = 0.35$, and follow-up pairwise comparisons revealed that in the superior frontal gyrus, both MCI and AD patients had higher retention in comparison to controls (MCI: $p = .049$; AD: $p = .036$). In the middle frontal gyrus and anterior cingulate cortex, there were non-significant trends for higher retention in MCI patients in comparison to controls ($p = .063$, $p = .075$, respectively), and significantly higher retention in AD patients in comparison to controls ($p = .025$, $p = .049$, respectively). In the superior parietal lobule, AD patients showed higher PiB retention ($p = .035$ vs. NECs). Finally, MCI patients had higher PiB retention than AD patients in the hippocampus ($p = .040$), and there were no significant group differences for the parahippocampal gyrus.

2.4.8 Correlational Analysis

In order to examine the relationship between the various neuroimaging measures (EEG coherence, cortical thickness, and PiB retention) and between EEG coherence and measures of cognitive performance, we computed several exploratory Pearson correlations. We examined EEG coherence for electrode pairs of interest (F3-F4, P3-P4, F3-P3) for all frequency bands. We ran two sets of correlational analyses: (1) correlations for EEG coherence with cortical thickness and PiB retention, and (2) correlations between EEG coherence and neuropsychological test performance (MoCA, CVLT delayed recall, LNS, Stroop test, Hayling Test). We consider these data to be exploratory in nature due to the large number of correlations computed as well as the small sample size. As we were interested in exploring the relationship between these various measures in each of the individual groups, the sample size for the correlations is often quite small (e.g., $n = 7$ for any correlations with cortical thickness or PiB retention values for AD patients; refer to sample sizes noted in the presentation of the above results). Nevertheless, several reliable correlations emerged in our examination of the data.

2.4.8.1 EEG coherence, cortical thickness, and PiB retention. First, we examined the relationship between EEG coherence and both cortical thickness and PiB retention. A summary of the significant correlations is presented in Table 2.7. Several notable patterns can be observed in this table. First, there were virtually no correlations between these variables for AD patients. Second, for NECs and MCI patients, there were several reliable correlations between EEG coherence and PiB retention, but only one reliable correlation in each group for cortical thickness. Third, there was very little overlap across groups in which EEG coherence variables were reliably correlated with cortical thickness and PiB.

2.4.8.1.1 EEG coherence and cortical thickness. There were few reliable correlations between EEG coherence and cortical thickness (only one in each group), and there does not appear to be a consistent pattern across groups. However, the correlations that were significant are very large in magnitude for NECs and AD patients.

2.4.8.1.2 EEG coherence and PiB retention. Sample scatterplots for the relationship between EEG coherence and PiB retention in NECs and MCI patients are presented in Figure 2.5. As can be seen in the left panels of this figure and in Table 2.7, in normal controls, higher coherence in cross-hemisphere pairs was associated lower with PiB retention in the superior parietal lobule (parietal theta) and the frontal cortex (parietal alpha and frontal beta). In contrast, higher intrahemispheric fronto-parietal coherence was associated with higher PiB retention in the frontal cortex, anterior cingulate cortex, and hippocampus (theta) and parahippocampal gyrus (gamma). For correlations that did not reach statistical significance, this general pattern held true across frequency bands: higher cross-hemisphere coherence was associated with lower PiB retention, whereas higher fronto-parietal coherence was associated with higher retention.

In contrast to the pattern seen in NECs, for MCI patients, higher coherence was associated with lower PiB retention for both cross-hemisphere frontal and intrahemispheric pairs (see right panels in Figure 2.5). There were no reliable associations with the cross-hemisphere parietal pair. Higher cross-hemisphere frontal coherence was associated with lower PiB retention in the frontal cortex (theta and gamma), anterior cingulate cortex (theta, beta, gamma), superior parietal lobule (theta and gamma), hippocampus (gamma), and parahippocampal gyrus (beta and gamma). Higher fronto-parietal beta coherence was associated with lower retention in the frontal cortex (though the correlations did not reach statistical significance, the same pattern was observed for the theta and gamma bands).

There were no reliable associations between resting coherence and PiB retention in AD patients.

Thus, though the correlations did not always reach statistical significance, several consistent patterns emerged: (1) Higher cross-hemisphere frontal coherence was associated with lower PiB retention in both normal controls and MCI patients. For normal controls, this pattern was seen in higher frequency bands (particularly beta and gamma) in association with PiB retention in frontal areas. For MCI patients, this pattern was seen across all frequency bands and PiB retention ROIs. (2) Higher cross-hemisphere parietal coherence in theta, alpha, beta, and gamma bands was associated with lower PiB retention in frontal and parietal regions in normal controls. There was no association between cross hemisphere parietal coherence and PiB retention in MCI patients. (3) Higher intrahemispheric fronto-parietal coherence in all frequency bands was associated with higher PiB retention in frontal regions in normal controls. In contrast, higher fronto-parietal coherence in theta, beta, and gamma bands was associated with lower PiB retention in frontal regions in MCI patients.

2.4.8.2 EEG coherence and neuropsychological test performance. The relationships between EEG coherence and neuropsychological test performance are presented in Table 2.8. The neuropsychological measures examined were: MoCA score, CVLT delayed recall score, LNS score, Stroop inhibition time, Stroop errors, Hayling Test inhibition time, and Hayling Test errors. There were few reliable correlations between EEG coherence and neuropsychological test performance in NECs and MCI patients. In some instances, higher coherence was associated with poorer test performance (e.g., higher frontal gamma coherence was associated with more errors on the Hayling test in normal controls), and in some instances higher coherence was associated with better test performance (e.g., higher frontal gamma coherence was associated with lower time on the Stroop test in MCI patients). Overall, there does not appear to be a striking relationship between resting coherence and neuropsychological test performance in NECs or MCI patients. In contrast, there were several reliable correlations between resting coherence and test performance in AD patients. Generally speaking, higher coherence was associated with better test performance (the two exceptions are alpha F3-P3 coherence and Stroop errors and gamma P3-P4 coherence and LNS score). Better performance on CVLT delayed recall was associated with higher frontal and fronto-parietal coherence in the beta and gamma bands. Better performance on the LNS test was associated with higher parietal

coherence in the delta and gamma bands. Finally, better performance on the Hayling test was associated with higher frontal coherence in the delta, theta, and alpha bands, higher parietal coherence in the theta, alpha, and beta bands, and higher fronto-parietal coherence in the theta and alpha bands.

2.4.9 MCI Converters vs. Non-Converters

Though power was limited due to small sample sizes, several differences were noted between stable MCI patients (n = 9) and those who converted to dementia (n = 7). MCI patients who converted had significantly higher education, $F(1, 14) = 9.09$, $p = .009$, $\eta^2_p = 0.39$ (MCI-c: $M = 17.14$, $SD = 3.81$; MCI-s: $M = 12.89$, $SD = 1.69$). There were also significantly more males in the MCI converter group, $\chi^2(1, N = 16) = 3.87$, $p = .049$ (MCI-c: 71% males; MCI-s: 22% males). There were no significant differences for age, GDS score, SMCS score, or MoCA score. With regards to neuropsychological test scores, there was a trend for lower CVLT delayed recall scores in MCI converters, $F(1, 14) = 3.23$, $p = .094$, $\eta^2_p = 0.19$ (MCI-c: $M = 2.57$, $SD = 2.26$; MCI-s: $M = 5.56$, $SD = 3.91$). There were no other group differences on the neuropsychological tests (due to missing data, there was an insufficient number of participants to evaluate group differences for the Trail Making Test and Stroop Test).

With regards to EEG coherence, the only group difference was a significant group x electrode pair interaction for intrahemispheric pairs in the gamma band, $F(1, 14) = 9.05$, $p = .009$, $\eta^2_p = 0.39$. Pairwise comparisons revealed that the group difference was significant only for F3-P3 ($p = .031$), where coherence was higher for MCI-c ($M = .377$, $SE = .045$) in comparison to MCI-s ($M = .232$, $SE = .040$).

2.5 Discussion

The main goal of the present study was to examine the relationship between EEG coherence and measures of cognition and neuropathology in MCI and AD. We examined group differences on neuropsychological tests, resting state spectral EEG power, resting state EEG coherence within a fronto-parietal network, cortical thickness, and PiB retention. In addition, we compared baseline measures of neuropsychological test performance and EEG coherence between MCI patients who converted to dementia and those who remained stable over a period of approximately two to four years. Finally, we conducted a number of exploratory correlations between EEG coherence and neuroimaging and neuropsychological variables.

2.5.1 Group Differences

Neuropsychological testing confirmed that our MCI and AD patients showed a pattern of cognitive deficits typical of these groups. AD patients exhibited deficits on measures of verbal episodic memory, verbal abstract reasoning, visuomotor processing speed, short-term memory span, confrontational naming, working memory, semantic and phonemic verbal fluency, and inhibitory control. MCI patients showed deficits on measures of verbal episodic memory, verbal abstract reasoning, visual processing speed, semantic verbal fluency, and inhibitory control.

2.5.1.1 Alzheimer's disease. Turning now to group differences on EEG measures, AD patients showed reduced posterior power in the beta band relative to normal controls, consistent with previous literature (e.g., de Haan et al., 2008; Ranasinghe et al., 2014); however, in our sample, the tendency towards reduced alpha power did not reach statistical significance due to high inter-individual variability. Furthermore, we did not find enhanced delta and theta power as has been reported in previous studies (e.g., Adler et al., 2003; de Haan et al., 2008; Fonseca et al., 2013; Huang et al., 2000).

With respect to EEG coherence, we predicted a widespread decrease in coherence in AD patients based on the previous literature (C. Babiloni et al., 2011; 2015); however, we found that coherence was reduced only for the cross-hemisphere parietal pair in the delta and theta bands and the cross-hemisphere occipital pair in the delta band. There was also a tendency towards reduced cross-hemisphere frontal coherence in the alpha band.

For measures of cortical thickness and PiB retention, as expected, we found reduced cortical thickness in the parahippocampal gyrus and the anterior cingulate cortex and higher PiB retention in the superior frontal gyrus, middle frontal gyrus, anterior cingulate cortex, and superior parietal lobule.

2.5.1.2 Mild cognitive impairment. With respect to EEG power, we predicted that MCI patients would exhibit reduced power in the alpha band; however, though MCI patients showed a tendency towards lower alpha power, this difference did not reach statistical significance. MCI patients did, however, show significantly reduced beta power at central, parietal, and occipital sites.

With regards to EEG coherence, we predicted reduced fronto-parietal coherence across frequency bands based on previous literature (C. Babiloni, Ferri, et al., 2006b; Moretti et al., 2008); however, we did not find any differences in coherence between MCI patients and controls.

The literature in this area is mixed, however, and other studies have also reported no differences between MCI patients and controls using measures of coherence and synchronization (Jiang et al., 2008; Stam et al., 2003).

Finally, as expected, we found reduced cortical thickness in the parahippocampal gyrus and higher PiB retention in the superior frontal gyrus, as well as a tendency towards higher PiB retention in the middle frontal gyrus and anterior cingulate cortex.

In our analysis of MCI patients who progressed to dementia versus those who remained stable after a follow-up period of approximately three years, we found that there was a trend for lower CVLT delayed recall scores and significantly higher fronto-parietal gamma coherence for MCI converters. Higher fronto-parietal coherence in MCI converters has been previously reported in several frequency bands (Rossini et al., 2006). The authors interpreted this finding as a reflection of cholinergic impairment, which alters reciprocal inhibition between the delta and alpha bands and results in an unselective increase in power and coherence across frequency bands. It is also possible that this represents a process that is compensatory in the short term, but predictive of decline in the long term. Longitudinal studies would be required in order to test this hypothesis.

2.5.2 Correlational Analyses

We performed correlational analyses in order to explore the relationship between EEG coherence and other measures of neuropathology (cortical thickness and PiB retention) as well as between EEG coherence and cognition. With respect to the relationship between coherence and neuropathology, we found that EEG coherence was reliably associated with PiB retention, but not with cortical thickness. In the present study, we did not find group differences in cortical thickness in frontal or parietal areas. Therefore, the absence of a reliable association between coherence and cortical thickness may be due to the lack of disease-related atrophy in frontal and parietal areas. That is, cortical thickness is not reduced enough to have an impact on functional connectivity. PiB retention, on the other hand, was increased in our patient sample in frontal and parietal regions, thus amyloid deposition in these areas is reflective of a neuropathological process that one might expect to have an impact on functional connectivity within a fronto-parietal network. There were some interesting patterns in the relationship between EEG coherence and PiB retention in normal controls and MCI patients, but PiB retention was not reliably associated with coherence in AD patients. However, the sample size for AD patients for

correlations with PiB variables was small (n = 7), and several large correlations failed to reach statistical significance. For example, correlations greater than 0.60 ($p < .15$) between gamma band coherence and PiB retention suggest a positive association between gamma frontal and fronto-parietal coherence and PiB retention in the prefrontal cortex and a negative association between gamma parietal coherence and PiB retention in the hippocampus. Future studies with larger sample sizes would help to clarify whether there is a reliable association between EEG coherence and PiB retention in AD patients.

With respect to the relationship between EEG coherence and PiB retention in normal controls, cross-hemisphere frontal (beta) and parietal (theta and alpha) coherence was negatively correlated with PiB retention, whereas intrahemispheric fronto-parietal coherence (theta and gamma) was positively correlated with PiB retention. Thus, in normal controls, increased amyloid burden is associated with decreased inter-hemispheric coherence, but increased fronto-parietal coherence. One might speculate that increasing fronto-parietal coherence with increasing amyloid burden may be reflective of a compensatory process. However, the interpretation of increased functional connectivity is difficult, as it could be a reflection of compensation, neural inefficiency, or both. According to the compensation-related utilization of neural circuits hypothesis, or CRUNCH (Reuter-Lorenz & Lustig, 2005), compensatory increased activation of neural circuits would be associated with improved, or at least maintained, cognitive performance. Theoretically, if coherence is increased only to the extent necessary to overcome pathological burden and maintain normal cognitive performance, then no correlation between coherence and cognition would be expected (i.e., whether moderate or large increases in coherence are needed to maintain performance, the result is a similar level of performance). Conversely, dedifferentiation, or the non-selective recruitment of brain areas, would be associated with poorer cognitive performance.

In our sample of normal elderly controls, resting fronto-parietal coherence in the theta and gamma bands was not reliably related to selected measures of cognition. Thus, as we were not able to demonstrate that increased coherence is associated with poorer performance, these results are more consistent with compensation than dedifferentiation. The increased coherence with increasing amyloid burden may be reflective of compensatory processes that allows for the maintenance of normal cognitive performance, despite increased pathological burden. However,

this interpretation is speculative, and future studies examining intra-individual changes in the relationship between these variables over time are needed in order to clarify this issue.

Interestingly, in contrast to normal controls, where intrahemispheric fronto-parietal theta and gamma coherence were associated with PiB retention, MCI patients did not show a reliable association between these variables. In MCI patients, PiB retention was primarily associated with cross-hemisphere frontal coherence, such that higher PiB retention was associated with lower frontal coherence (theta, beta, and gamma bands). In the beta band, higher PiB retention was also associated with lower fronto-parietal coherence. Thus, while higher PiB retention was associated with lower cross-hemisphere frontal coherence in both normal controls and MCI patients, opposite patterns were seen in normal controls and MCI patients for intrahemispheric fronto-parietal coherence. Specifically, higher PiB retention was associated with higher fronto-parietal coherence in normal controls, but with lower fronto-parietal coherence in MCI patients.

We were interested to know whether group differences in coherence for AD patients versus controls (reduced cross-hemisphere parietal in the delta and theta bands and cross-hemisphere occipital in the delta band) were related to other neuroimaging measures and/or to measures of cognitive performance. However, the coherence measures that were reduced in AD patients did not show a strong relationship with other variables. Parietal theta coherence was not related to cortical thickness or PiB retention; however, reduced parietal theta coherence was related to poorer performance on the Hayling test (lower response time and higher errors). The parietal cortex has been found to be related to tasks of inhibitory control in functional neuroimaging studies (Nee et al., 2007; Swick et al., 2011), and hypometabolism in parietal regions has been associated with performance on inhibition tasks in AD patients (Collette et al., 2002; Yun et al., 2011). Thus, the results of the present study, which show reduced resting-state cross-hemisphere parietal coherence in the theta band in AD patients that is related to poorer performance on a measure of inhibitory control, are in line with previous studies implicating functional changes parietal regions in deficits in inhibitory functioning in AD.

A striking pattern that emerged in these data, namely very strong correlations between EEG coherence and neuropsychological test performance in AD patients, but few correlations between these variables in normal controls and MCI patients. One possible interpretation for this pattern of results is that there is more variability in the way that functional brain connectivity is recruited to support cognitive functioning in healthy older adults and MCI patients in comparison

to AD patients. For example, healthy older adults and MCI patients may represent heterogeneous groups in which some individuals show lower connectivity due to neural efficiency (lower coherence related to better cognitive performance) and others who show higher connectivity due to compensatory processes (higher coherence related to better cognitive performance), thus obscuring the relationship between these variables within the groups. In contrast, AD patients may have reached a threshold of neuropathology where neural efficiency and compensatory processes can no longer be invoked, thus leading to a more consistent relationship between reduced connectivity and lower cognitive performance.

In AD patients, lower EEG coherence was most strongly related to poorer performance on the CVLT and the Hayling Test. Specifically, lower performance on CVLT delayed recall was associated with lower frontal and fronto-parietal coherence in the beta and gamma bands. Lower performance on the Hayling Test was associated with lower frontal coherence in the delta, theta, and alpha bands (errors), lower parietal coherence in the theta (time, errors), alpha (errors) and beta (time) bands, and lower fronto-parietal coherence in the theta and alpha bands (time). It is interesting that inhibitory control (Hayling test) was most strongly correlated with inter-hemispheric frontal and parietal coherence in the lower frequency bands (delta, theta, alpha), whereas episodic memory (CVLT) was most strongly correlated with inter-hemispheric frontal and intra-hemispheric fronto-parietal coherence in the higher frequency bands (beta and gamma).

The relationship between fronto-parietal connectivity and CVLT performance is consistent with a previous study that examined resting state fMRI connectivity (Liang et al., 2011). Furthermore, in a recent study that examined MEG coherence between specific brain regions and all other brain areas for the alpha band, lower functional connectivity of the frontal cortex was associated with poorer performance on tests of executive functioning (verbal fluency, digit span backwards, verbal learning) and episodic memory in AD patients (Ranasinghe et al., 2014). The results of the present study are consistent with this finding, in that CVLT performance was correlated with EEG coherence when it involved a frontal electrode (F3-F4 and F3-P3). However, we also found that cross-hemisphere parietal coherence was associated with performance on the Hayling test (in addition to cross-hemisphere frontal and fronto-parietal coherence). In contrast, in another study, intrahemispheric EEG coherence in the delta and theta bands was found to be negatively associated with performance on neuropsychological tests such as verbal fluency and word list memory (Fonseca et al., 2011). In the present study, fronto-

parietal coherence in the beta and gamma bands was positively correlated with CVLT performance. It is difficult to directly compare these studies due to different electrode pairs examined (fronto-parietal in the present study and averaged fronto-occipital, centro-parietal and temporo-temporal in Fonseca et al., 2011); however, it is possible that intrahemispheric EEG coherence has an inverse relationship with cognition for lower frequency bands and a positive relationship with cognition for higher frequency bands. Future research is needed to clarify this issue. It is interesting to note, however, that as was the case in the present study, Fonseca et al. (2011) also found reliable associations between EEG coherence and cognition for AD patients but not for normal controls. Thus, we have confirmatory evidence that EEG coherence may be directly related to cognition only for individuals who exhibit a breakdown in both neural and cognitive functioning.

2.5.3 Summary, Conclusions, and Future Directions

This is the first study to our knowledge to examine the relationship between EEG coherence, cognition, cortical thickness, and PiB retention. A major limitation of the present study is the small sample size for the correlational analysis, particularly for cortical thickness and PiB retention for AD patients and controls. Nevertheless, several interesting trends emerged in the data that warrant further investigation. First, with regards to group differences, we found reduced spectral EEG power in the beta band for both MCI patients and AD patients, and reduced posterior coherence in the delta and theta bands for AD patients only. This suggests that changes in EEG power may be detectable at an earlier stage than changes in resting coherence. There is some evidence to suggest that measuring coherence during the performance of a cognitive task is more sensitive to detecting differences in MCI patients (Jiang et al., 2008), therefore future studies examining coherence during task performance are warranted. We are examining this issue by investigating EEG coherence during the performance of tasks of inhibitory control and working memory in patients with MCI and AD (Johns & Phillips, 2015a; 2015b).

Second, in both NECs and MCI patients, higher PiB retention was associated with lower cross-hemisphere frontal coherence, and in NECs, higher PiB retention was additionally associated with lower cross-hemisphere parietal coherence and higher fronto-parietal coherence. It is possible that this increase in fronto-parietal coherence in association with increased amyloid burden in normal controls is a compensatory process that enables certain individuals to maintain

normal cognitive functioning, but which breaks down in the transition to MCI and AD. This is an interesting, though speculative, hypothesis that could be further investigated in longitudinal studies in which both PiB retention and EEG coherence are measured at multiple time points through the progression from normal cognitive functioning to cognitive impairment.

Finally, resting EEG coherence showed a reliable relationship with cognition only for AD patients. Specifically, lower cross-hemisphere frontal and parietal coherence in lower frequency bands was related to poorer inhibitory control (Hayling test), and lower frontal and fronto-parietal coherence in higher frequency bands was related to poorer episodic memory (CVLT). These results provide interesting preliminary evidence for cross-hemisphere functional connection in frontal and parietal regions as a potential neural mechanism underlying executive dysfunction in AD patients. Furthermore, these results point to a potential role of reduced frontal and fronto-parietal coherence in contributing to episodic memory dysfunction in AD.

In addition to the small sample size noted above, a few additional limitations of the present study warrant mention. First, there was a time delay between the measurement of EEG coherence and cortical thickness and PiB. Due to practical constraints, MRI and PiB scans were performed within one year of EEG testing for MCI patients and within two years of EEG testing for normal controls and AD patients, therefore it is possible that neuropathological changes occurred between the two testing sessions, which could have affected correlations between these variables. Future studies examining the relationship between EEG coherence and neuropathology with measurements taken closer in time would be beneficial. In addition, it is important to note that, given the relatively low spatial resolution of EEG, we cannot be exact about which specific brain regions give rise to the signal recorded at a particular electrode site. However, we have assumed that activity recorded at frontal sites reflects primarily frontal cortical activity, and activity recorded at parietal sites reflects primarily parietal cortical activity.

This study contributes to the growing literature on quantitative EEG measurements in MCI and AD by beginning to examine the relationships between multiple cognitive and neuropathological markers. Continued research in this area will hopefully result in an increased understanding of the role of functional neural networks in the neuropathology of AD. Furthermore, as EEG is an inexpensive and non-invasive procedure, it continues to hold promise as a screening tool for early diagnosis, should reliable measures be discovered for the earliest stages of the disease.

Table 2.1.

Summary of Studies of Resting State Synchronization in AD Patients Versus Normal Controls

	Delta		Theta		Alpha		Beta		Gamma	
	↓	n.s.	↓	n.s.	↓	n.s.	↓	n.s.	↓	n.s.
Global[l]		a, b, c		a, b, c	a, c	b	a, b, c		c	a, b
Cross-hemisphere (any pair)	d, e, g, i, j, k	f, h	d, e, i, j, k	f, g, h	d, e, f, g, h, i, j	k	e, f, g, i, j	d, h, k	e	k
Cross-hemisphere										
Frontal	e, k	d, f, g, i, j	k	d, e, f, g, i, j	f, g, i, j	d, e, k	e, f, g, j	d, i, k	e	k
Central	d, e, i	g, h, j, k	d, e, i, j	g, h, k	e, h, i, j	d, g, k	e, i, j	d, g, h, k	e	k
Temporal	i, j	d, f, g, h	i, j	d, f, g, h	h, i, j	d, f, g	i, j	d, f, g, h		
Parietal	e, i, j	d, g, h, k	d, e, i, j	g, h, k	d, e, h, i, j	g, k	e, i	d, g, h, j, k	e	k
Occipital	d, i	f, g, h, j	d,	f, g, h, i, j	d, j	f, g, h, i		d, f, g, h, i, j		
Long-distance Intrahemispheric (any pair)	e, i, k	f, g, h, l	e, h	f, g, i, k, l	e, h, k, l	f, g, i	l	e, f, g, h, i, k	m	e, k
Long-distance Intrahemispheric										
Fronto-parietal	e, k	l	e	k, l	e, k, l		l	e, k		e, k, m
Fronto-temporal									m	
Fronto-occipital	i	f, g		f, g, i		f, g, i		f, g, i		m
Temporo-occipital		h	h		h			h		
Local (any pair)	d, i	g, l	d, i	g, l	d	g, i,				m
Local										
Frontal		d, l		d, l		d, l		d, l		m
Central		d		d		d		d		
Temporal	d, i	g	d, i	g	d	g, i	d	g, i		
Parietal	d			d	d					

Note. [1]Global synchronization measures are computed in various ways and result in one overall measurement for each frequency range. [a]Koenig et al., 2005; [b]Ma et al., 2014; [c]Stam et al., 2002; [d]Adler et al., 2003; [e]Babiloni et al., 2004b; [f]Fonseca et al., 2013; [g]Fonseca et al., 2011; [h]Jiang, 2005a; [i]Knott et al., 2000; [j]Wada et al., 1998b; [k]Babiloni, Ferri, et al., 2006b; [l]Leuchter et al., 1992; [m]Tao & Tian, 2005.

Table 2.2.

Summary of Studies of Resting State Synchronization in MCI Patients Versus Normal Controls

	Delta			Theta			Alpha			Beta			Gamma		
	↑	↓	n.s.	↑	↓	n.s.	↑	↓	n.s.	↑	↓	n.s.	↑	↓	n.s.
Global[a]			a, b			a, b			a, b		a, b			a	b
Cross-hemisphere (any pair)	d	c	f, h	d	c	f, h	d	f, i	c, h			c, d, f, h, i			c, d, f
Cross-hemisphere															
Frontal	d	c	f, h		c	d, f, h		f	c, d, h, i			c, d, f, h, i			c, d, f
Central	d		c, f, h	d		c, f, h	d		c, f, h			c, d, f, h			c, d, f
Temporal			f, h			f, h			f, h			f, h			f
Parietal			c, f, h			c, f, h			c, f, h			c, f, h			c, f
Temporal, parietal, central average								i				i			
Occipital			f, h			f, h			f, h			f, h			f
Long-distance Intrahemispheric (any pair)		c, d, e	f		d	c, e, f		c, d, f	e		d	c, e, f		d	c, e, f, g
Long-distance Intrahemispheric															
Fronto-parietal		c, d, e	f		d	c, e, f		c, d, f	e		d	c, e, f		d	c, e, f, g
Fronto-temporal		e	d, f			d, e, f			d, e, f			d, e, f			d, e, f, g
Fronto-occipital			f			f		f				f			f, g
Temporo-occipital			f			f			f			f			f
Local (any pair)		e				e	e					e			e
Local															
Frontal		e				e			e			e			e
Temporal			e			e			e			e			e
Parietal			e			e	e					e			e

Note. [1]Global synchronization measures are computed in various ways and result in one overall measurement for each frequency range. [a]Gómez et al, 2009; [b]Koenig et al., 2005; [c]Babiloni, Ferri, et al., 2006b; [d]Moretti et al., 2008; [e]Tóth et al., 2014; [f]Xu et al., 2014; [g]Tao & Tian, 2005; [h]Jiang et al., 2008; [i]Teipel et al., 2009.

Table 2.3.
Demographic and Clinical Variables

	NEC (n = 26)		MCI (n = 21)		AD (n = 16)		Group
Variable	*M*	*SD*	*M*	*SD*	*M*	*SD*	Differences
Age	78.2	4.4	80.2	5.7	79.7	5.5	n.s.
Education	14.4	4.0	13.7	4.1	13.8	2.9	n.s.
Sex (% Female)	57.7	--	52.4	--	25.0	--	n.s.
GDS	1.4	1.7	1.6	1.7	2.0	1.7	n.s.
SMCS	3.1	2.7	4.7	2.4	6.8	5.4	AD>NEC
MoCA	27.6	1.5	22.5	4.3	19.3	4.3	AD<MCI<NEC

Note. NEC = normal elderly controls; MCI = mild cognitive impairment; AD = Alzheimer's disease; GDS = Geriatric Depression Scale; SMCS = Subjective Memory Complaints Scale; MoCA = Montreal Cognitive Assessment.

Table 2.4.
Neuropsychological Test Scores

Variable	NEC			MCI			AD			Group Differences[a]
	n	*M*	*SD*	*n*	*M*	*SD*	*n*	*M*	*SD*	
Similarities (Total /33)	26	24.5	4.4	21	19.1	4.3	16	17.4	6.6	AD=MCI<NEC
Symbol Search (Total /60)	26	25.4	5.4	19	19.5	7.3	16	13.9	9.2	AD<MCI<NEC
Digit Span Forward (Total /16)	26	6.6	1.2	11	5.6	1.6	14	5.1	0.9	AD<NEC[b]
Digit Span Backwards (Total /14)	26	5.1	1.4	11	4.1	1.3	14	4.1	0.9	n.s.[c]
Boston Naming Test (Total /15)	26	13.7	1.5	21	12.3	3.7	16	8.9	3.5	AD<MCI=NEC
CVLT Total Learning Trials (max /80)	26	46.0	7.0	21	30.8	8.2	16	22.2	7.2	AD<MCI<NEC
CVLT Long Delay (max /16)	26	10.3	3.2	21	3.9	3.6	16	1.3	1.9	AD<MCI<NEC
Letter Number Sequencing (Total /21)	26	9.9	3.0	12	8.1	1.7	12	6.6	3.2	AD<NEC[b]
Phonemic Fluency (Total Words: FAS)	25	42.5	10.9	20	36.2	11.8	16	29.8	12.5	AD<NEC
Semantic Fluency (Total Words: Animals)	25	17.8	4.1	20	12.7	4.3	16	9.1	4.3	AD<MCI<NEC
Trail Making Test Time in sec. (B/A)	22	2.8	1.5	14	2.8	1.1	14	4.0	2.9	n.s.[c]
Stroop Victoria Time in sec. (Colour/Dots)	26	1.8	0.5	13	2.2	0.7	14	2.1	0.5	n.s.
Stroop Victoria Errors (Colour - Dots)	26	0.1	0.4	13	1.7	2.1	14	2.6	4.3	AD>NEC
Hayling Test Time in sec. (Condition 2/1)	25	8.3	6.7	18	8.9	6.3	14	4.6	8.8	n.s.
Hayling Test Errors Scaled Score[d]	25	7.0	1.6	18	4.9	2.6	14	4.1	2.7	AD=MCI<NEC
Hayling Test Total Scaled Score	25	5.8	1.4	18	4.4	1.9	14	2.2	1.6	AD<MCI<NEC

Note. Due to a change in the procedure for the administration of the neuropsychological test battery at the memory clinic during the period of data collection for this study, certain neuropsychological tests are missing data for some participants, as indicated in the table above. NEC = normal elderly controls; MCI = mild cognitive impairment; AD = Alzheimer's disease; CVLT = California Verbal Learning Test. [a]Group differences noted in this column are at a significance level of $p < .05$. [b]$p < .10$ for MCI<NEC. [c]$p < .10$ for AD<NEC. [d]Higher scores indicate better performance.

Table 2.5.

ANOVA Results: EEG Coherence for Cross-Hemisphere Homologous Pairs

	F	df	*p*	η^2_p	ε	sig.
Delta						
Electrode Pair	129.68	2, 120	<.001	.68	.850	**
Group	4.54	2, 60	.015	.13	--	*
Electrode Pair x Group	0.09	4, 120	.978	.00	.850	
Theta						
Electrode Pair	297.21	2, 120	<.001	.83	.829	**
Group	2.62	2, 60	.081	.08	--	+
Electrode Pair x Group	0.99	4, 120	.406	.03	.829	
Alpha						
Electrode Pair	218.03	2, 120	<.001	.78	.866	**
Group	2.45	2, 60	.095	.08	--	+
Electrode Pair x Group	0.77	4, 120	.531	.03	.866	
Beta						
Electrode Pair	438.15	2, 120	<.001	.88	n.s.	**
Group	0.65	2, 60	.526	.02	--	
Electrode Pair x Group	1.71	4, 120	.152	.05	n.s.	
Gamma						
Electrode Pair	160.92	2, 120	<.001	.73	n.s.	**
Group	0.56	2, 60	.573	.02	--	
Electrode Pair x Group	1.96	4, 120	.105	.06	n.s.	

Note. ** $p < .01$. * $p < .05$. + $p < .10$.

Table 2.6.

ANOVA Results: EEG Coherence for Long Distance Intrahemispheric Pairs

	F	df	*p*	η^2_p	sig.
Delta					
Electrode Pair	89.55	1, 60	<.001	.60	**
Group	0.68	2, 60	.513	.02	
Electrode Pair x Group	0.28	1, 60	.756	.01	
Theta					
Electrode Pair	128.33	1, 60	<.001	.68	**
Group	0.38	2, 60	.683	.01	
Electrode Pair x Group	0.11	1, 60	.896	.00	
Alpha					
Electrode Pair	69.27	1, 60	<.001	.54	**
Group	0.80	2, 60	.455	.03	
Electrode Pair x Group	0.95	1, 60	.392	.03	
Beta					
Electrode Pair	104.67	1, 60	<.001	.64	**
Group	1.16	2, 60	.319	.04	
Electrode Pair x Group	0.70	1, 60	.503	.02	
Gamma					
Electrode Pair	153.13	1, 60	<.001	.72	**
Group	0.54	2, 60	.586	.59	
Electrode Pair x Group	0.04	1, 60	.961	.00	

Note. ** $p < .01$.

Table 2.7.

Correlations Between EEG Coherence and Cortical Thickness and PiB Retention

	Normal Elderly Controls			Mild Cognitive Impairment			Alzhiemer's Disease		
	Variables	***r***	***p***	**Variables**	***r***	***p***	**Variables**	***r***	***p***
EEG Coherence & Cortical Thickness	Gamma F3-F4 & Parahippocampal Gyrus	-.943	.001	Alpha P3-P4 & Superior Frontal Gyrus	.552	.022	Alpha F3-P3 & Anterior Cingulate Cortex	-.851	.015
EEG Coherence & PiB Retention	Beta F3-F4 & Superior Frontal Gyrus	-.637	.048	Theta F3-F4 & Superior Frontal Gyrus	-.674	.012	None		
	Beta F3-F4 & Middle Frontal Gyrus	-.647	.043	Theta F3-F4 & Middle Frontal Gyrus	-.673	.012			
				Theta F3-F4 & Anterior Cingulate Cortex	-.676	.011			
				Theta F3-F4 & Superior Parietal Lobule	-.644	.018			
				Beta F3-F4 & Anterior Cingulate Cortex	-.561	.046			
				Beta F3-F4 & Parahippocampal Gyrus	-.588	.035			
				Gamma F3-F4 & Superior Frontal Gyrus	-.595	.032			
				Gamma F3-F4 & Middle Frontal Gyrus	-.587	.035			
				Gamma F3-F4 & Anterior Cingulate Cortex	-.618	.024			
				Gamma F3-F4 & Superior Parietal Lobule	-.580	.038			
				Gamma F3-F4 & Hippocampus	-.604	.029			
				Gamma F3-F4 & Parahippocampal Gyrus	-.748	.003			
	Theta P3-P4 & Superior Parietal Lobule	-.812	.004						
	Alpha P3-P4 & Superior Frontal Gyrus	-.668	.035						
	Alpha P3-P4 & Middle Frontal Gyrus	-.643	.045						
	Theta F3-P3 & Superior Frontal Gyrus	.656	.039						
	Theta F3-P3 & Middle Frontal Gyrus	.760	.011						
	Theta F3-P3 & Anterior Cingulate Cortex	.757	.011						
	Theta F3-P3 & Hippocampus	.699	.024						
				Beta F3-P3 & Superior Frontal Gyrus	-.589	.034			
				Beta F3-P3 & Middle Frontal Gyrus	-.561	.046			
	Gamma F3-P3 & Parahippocampal Gyrus	.676	.032						

Note. In each cell, significant correlations are grouped by electrode pair (F3-F4 is presented first, followed by P3-P4, then F3-P3).

Table 2.8.

Correlations Between EEG Coherence and Neuropsychological Test Performance

	Normal Elderly Controls			Mild Cognitive Impairment			Alzhiemer's Disease		
	Variables	***r***	***p***	**Variables**	***r***	***p***	**Variables**	***r***	***p***
EEG Coherence & Neuropsychological Tests							**Delta F3-F4 & Hayling Test Errors Scaled Score**	**.779**	**.002**
							Theta F3-F4 & Hayling Test Errors Scaled Score	**.713**	**.006**
							Alpha F3-F4 & Hayling Test Errors Scaled Score	**.786**	**.001**
							Beta F3-F4 & CVLT Delayed Recall	**.700**	**.004**
	Gamma F3-F4 & Hayling Test Errors Scaled Score	-.485	.012	Gamma F3-F4 & Stroop Time	-.595	.032	**Gamma F3-F4 & CVLT Delayed Recall**	**.796**	**<.001**
							Delta P3-P4 & LNS	.617	.019
							Theta P3-P4 & Hayling Test Time	.651	.016
							Theta P3-P4 & Hayling Test Errors Scaled Score	.575	.040
							Alpha P3-P4 & Hayling Test Errors Scaled Score	**.813**	**.001**
							Beta P3-P4 & Hayling Test Time	.601	.030
							Gamma P3-P4 & LNS	-.667	.018
							Theta F3-P3 & Hayling Test Time	**.723**	**.005**
	Alpha F3-P3 & CVLT Delayed Recall	-.415	.035				Alpha F3-P3 & Stroop Errors	.538	.047
	Alpha F3-P3 & Hayling Test Time	-.398	.049				Alpha F3-P3 & Hayling Test Time	.589	.034
	Beta F3-P3 & CVLT Delayed Recall	-.458	.019	Beta F3-P3 & LNS	-.582	.047	**Beta F3-P3 & CVLT Delayed Recall**	**.681**	**.005**
							Gamma F3-P3 & CVLT Delayed Recall	**.648**	**.009**

Note. In each cell, significant correlations are grouped by electrode pair (F3-F4 is presented first, followed by P3-P4, then F3-P3). A higher score on the Hayling test errors scaled score indicates better performance. Bolded entries indicate $p < .01$.

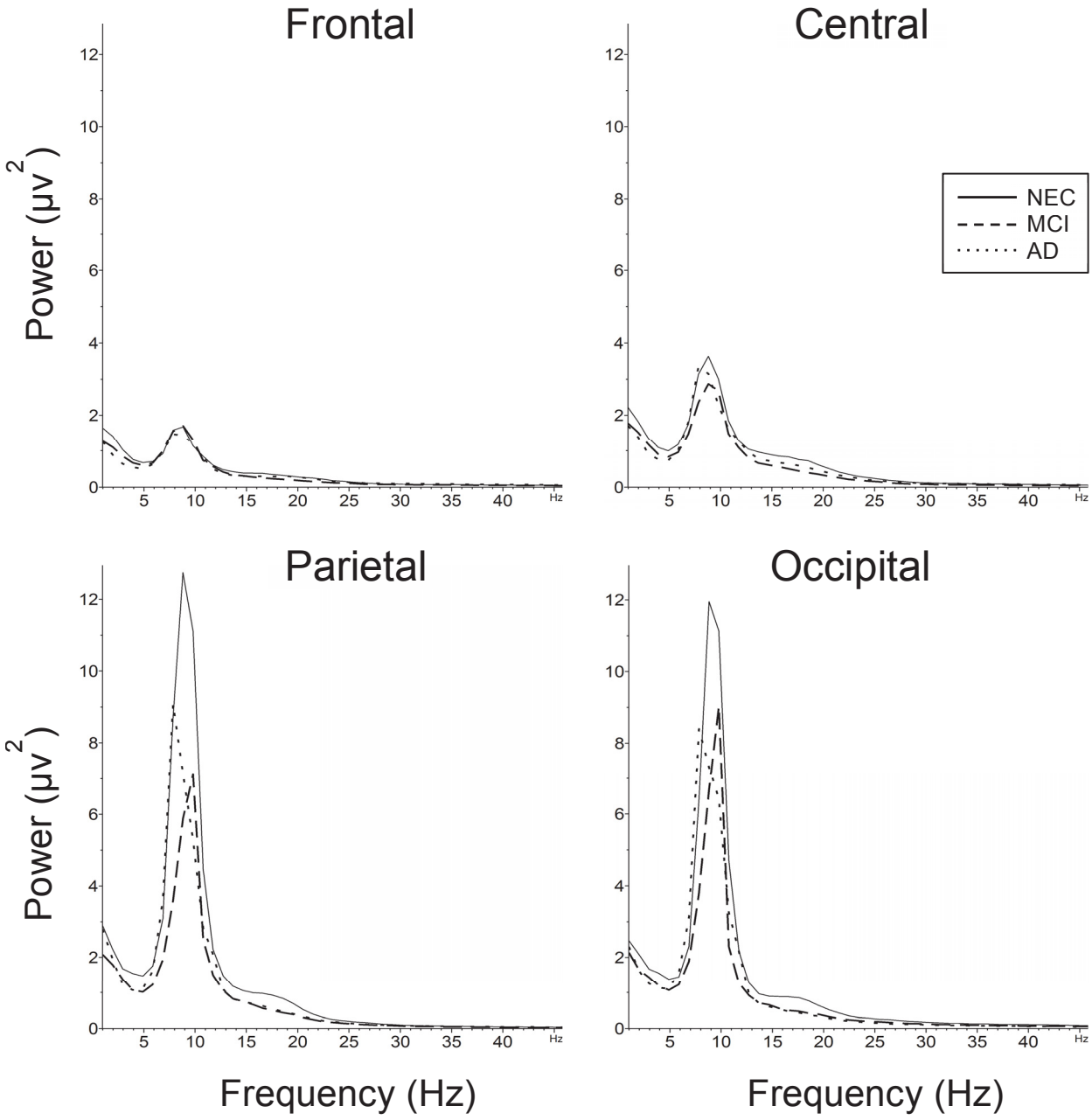

Figure 2.1. Mean closed eye EEG power at rest at frontal (F3, Fz, F4), central (C3, Cz, C4), parietal (P3, Pz, P4), and occipital (O1, O2) electrode sites for normal elderly controls (NEC), patients with mild cognitive impairment (MCI) and patients with Alzheimer's disease (AD).

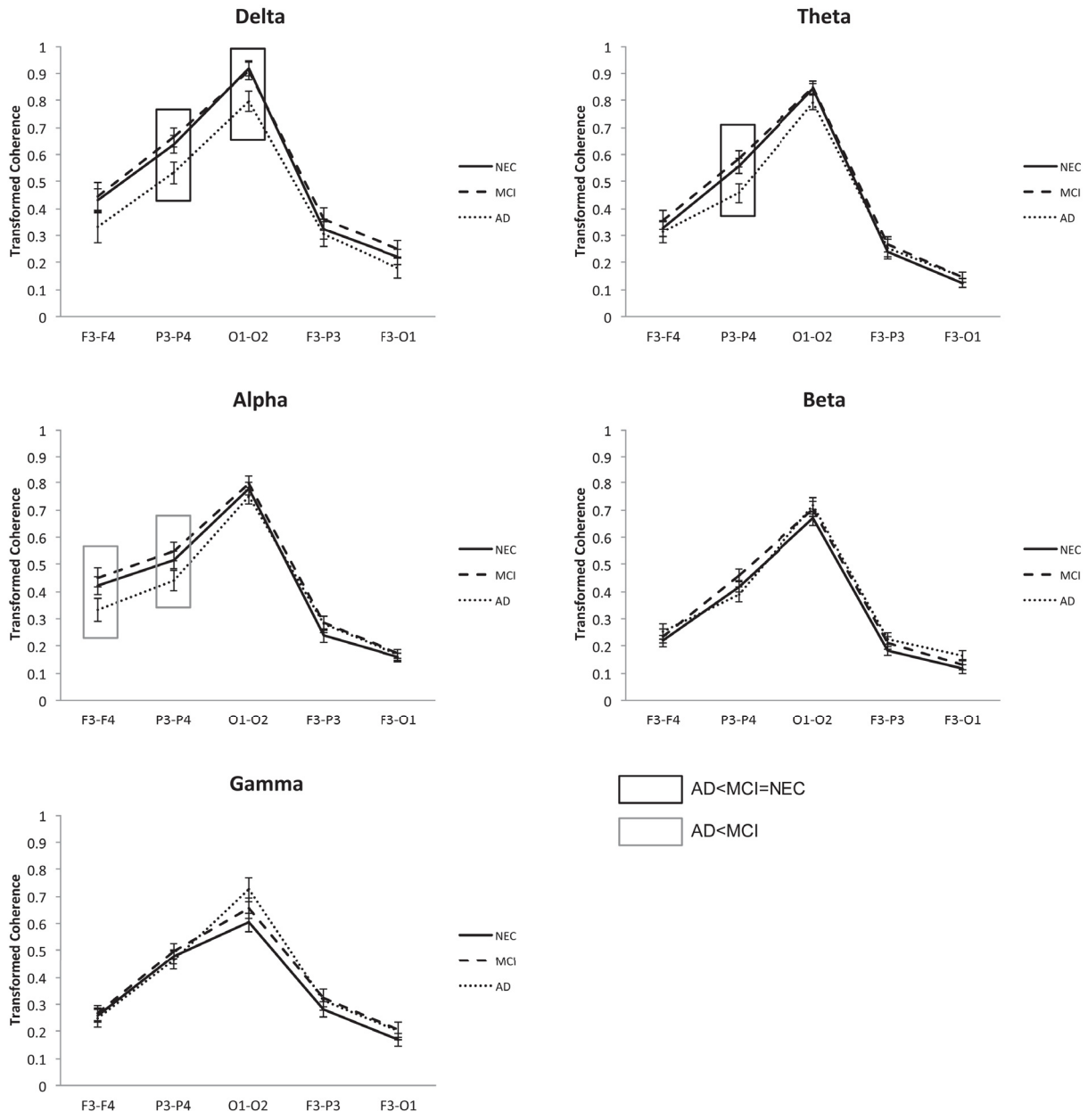

Figure 2.2. EEG coherence values for Normal Elderly Controls (NECs), patients with mild cognitive impairment (MCI), and patients with Alzheimer's disease (AD) during the eyes-closed resting condition. Data are square root and Fisher's Z transformed. Error bars represent the standard error of the mean.

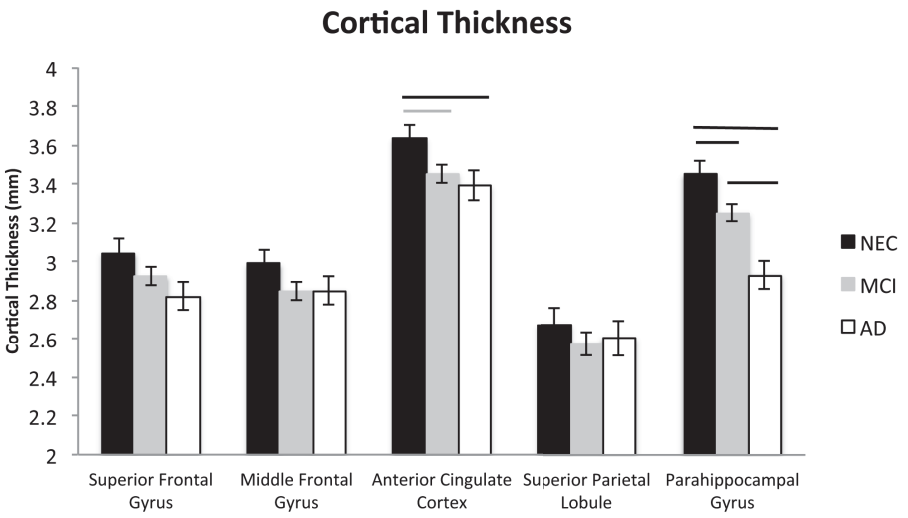

Figure 2.3. Cortical thickness for regions of interest for Normal Elderly Controls (NECs), patients with mild cognitive impairment (MCI), and patients with Alzheimer's disease (AD). Error bars represent the standard error of the mean. Black lines indicate significant group differences ($p < .05$). Grey lines indicate non-significant trends for a group difference ($p < .10$).

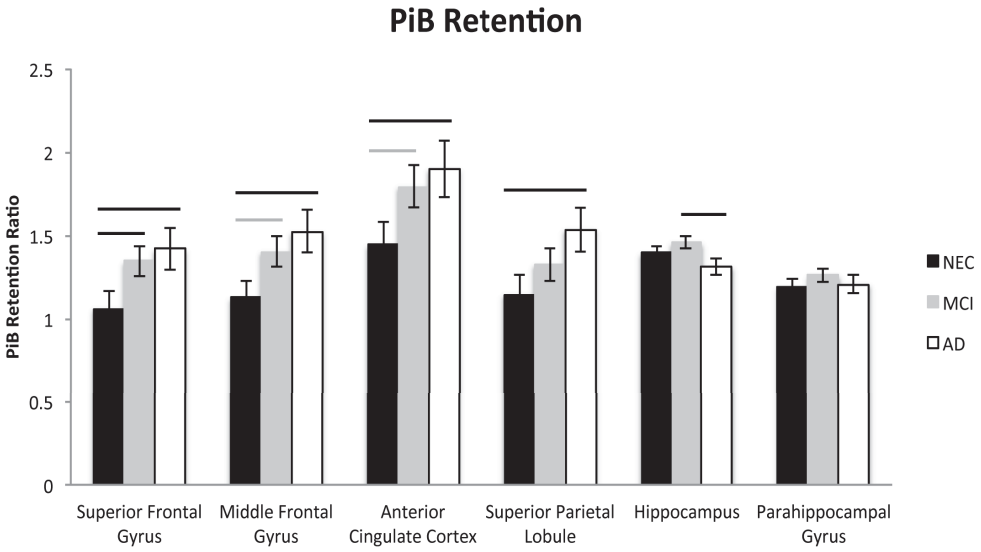

Figure 2.4. PiB retention for regions of interest for Normal Elderly Controls (NECs), patients with mild cognitive impairment (MCI), and patients with Alzheimer's disease (AD). Error bars represent the standard error of the mean. Black lines indicate significant group differences ($p < .05$). Grey lines indicate non-significant trends for a group difference ($p < .10$).

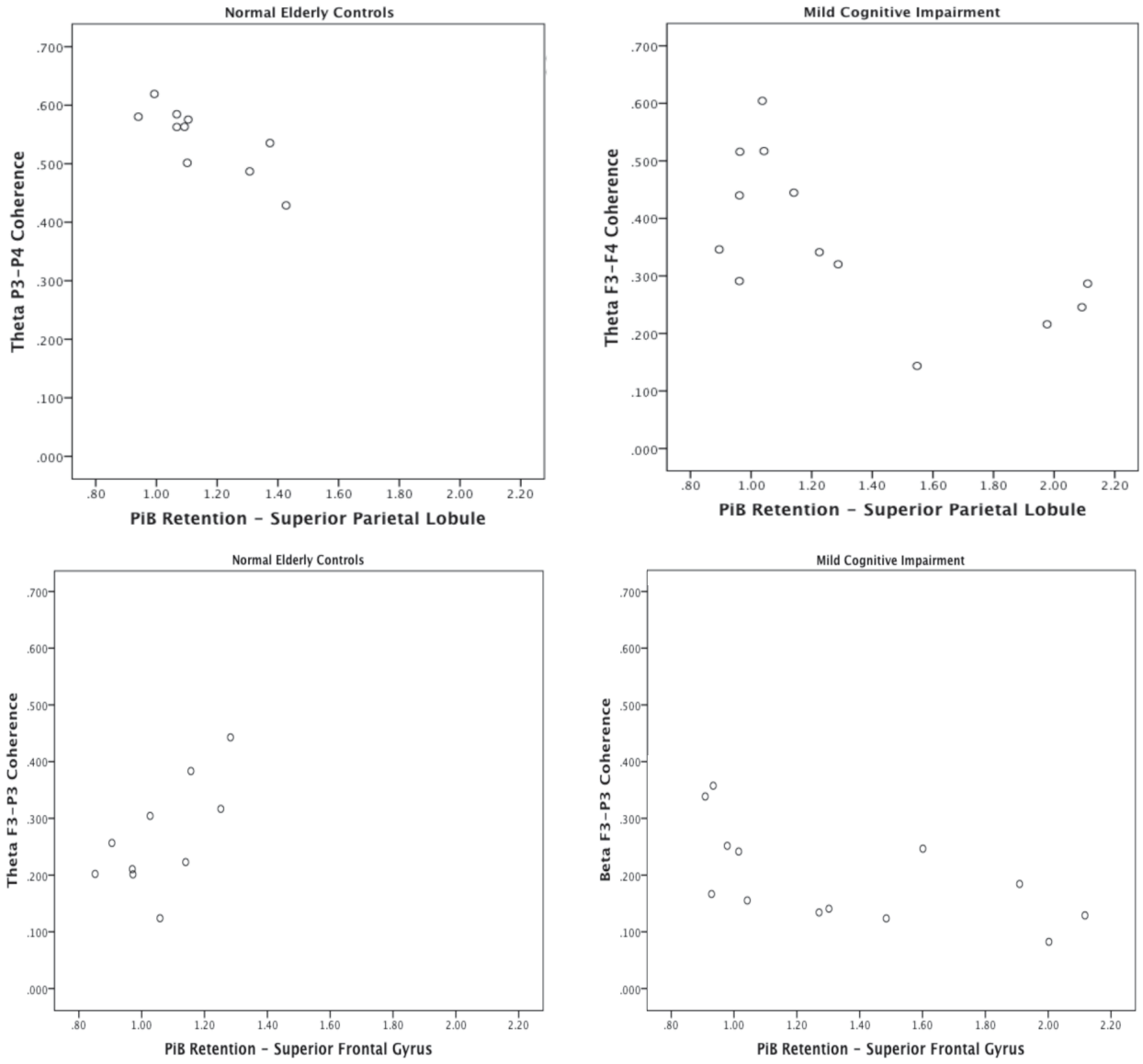

Figure 2.5. Sample scatterplots for EEG coherence and PiB retention in normal elderly controls and mild cognitive impairment. Cross-hemisphere coherence is represented in the top panels, and fronto-parietal coherence is represented in the bottom panels.

CHAPTER 3: STUDY 2

EEG Coherence and Inhibitory Control in
Mild Cognitive Impairment and Alzheimer's Disease

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3.1 Abstract

Objective: The primary goal was to examine the relationship between EEG coherence and inhibitory control in patients with mild cognitive impairment (MCI), Alzheimer's disease (AD), and normal elderly controls (NECs). *Methods:* We recorded EEG from 21 MCI patients, 16 AD patients, and 26 NECs during the performance of a Go/No-go task of inhibitory control. EEG coherence was calculated for a selection of electrode pairs within a fronto-parietal network for the delta, theta, alpha, beta, and gamma bands, and correlations between coherence, behavioural performance, and measures of brain integrity (cortical thickness and PiB retention) were explored. *Results:* Behavioural results showed that both AD patients and MCI patients had longer reaction times, but preserved accuracy on the Go/No-go task. EEG coherence increased for inhibition (No-go) trials in comparison to Go trials across electrode pairs, frequency bands, and groups. AD patients showed reduced cross-hemisphere theta coherence for frontal regions (No-go trials) and parietal regions (Go and No-go trials). Both AD and MCI patients showed less of a task-related increase of frontal theta coherence. Furthermore, MCI patients showed higher fronto-parietal alpha coherence during inhibition trials and a greater task-related increase in fronto-parietal alpha coherence. Correlations with measures of brain integrity were suggestive of a possible compensatory increase in coherence in MCI patients with increasing pathological burden. *Conclusion:* Functional connectivity within a fronto-parietal network is altered in both AD patients and MCI patients during the performance of a task of inhibitory control, with evidence of decreased cross-hemisphere connectivity in both groups, and an increase in intrahemispheric fronto-parietal connectivity (potentially compensatory) in MCI patients.

Keywords: Alzheimer's disease (AD), mild cognitive impairment (MCI), electroencephalography (EEG), EEG coherence, inhibitory control, Go/No-go, executive functioning, PiB, cortical thickness

3.2 Introduction

Executive dysfunction is increasingly being recognized as an important aspect of early Alzheimer's disease (AD) and mild cognitive impairment (MCI) (Johns et al., 2012; Perry & Hodges, 1999; Weintraub et al., 2012). However, the neural underpinnings of these deficits remain unclear. Executive functioning is a term that encompasses a number of different abilities in which higher level cognitive control is exercised over lower level cognitive functions (Diamond, 2013). The cognitive functions most often cited as components of executive functions include response inhibition, divided attention, working memory, planning, judgment, decision-making, and cognitive flexibility (Diamond, 2013; Goldstein et al., 2014; Stuss & Alexander, 2000; Stuss & Levine, 2002). Executive functions have long been linked to frontal lobe functioning; however it is now generally accepted that intact executive functioning depends on a distributed neural network involving both frontal and non-frontal regions (for reviews, see Collette et al., 2006; Gazzaley & D'Esposito, 2007; Stuss & Levine, 2002). Indeed, the control of lower level cognitive processes would necessitate the coordination of multiple brain regions, and numerous functional neuroimaging studies have found activation of the prefrontal cortex as well as posterior regions, mainly in the parietal cortex, during the performance of various tasks of executive function (for reviews, see Chung et al., 2014; Collette et al., 2006).

Inhibitory control, which is the focus of the present study, is an important aspect of executive functioning. Inhibitory control can be defined as the ability suppress or override a dominant, automatic response (Diamond, 2013). It is this ability to exert control over our own behaviour that enables us to choose our actions, rather than being driven by impulses and habit. Two commonly used tasks of inhibitory control are the Stroop test and the Go/No-go task. In the Stroop test, colour words are presented in a non-matching ink colour and participants are required inhibit the prepotent response of reading the word and instead name the colour of the ink. In the Go/No-go task, participants must provide a certain response (e.g., button press) for frequent stimuli (Go trials) and inhibit that same response for a particular infrequent stimulus (No-go trials). Two recent meta-analyses of neuroimaging studies that have examined the Stroop test and Go/No-go task found that the most significant activations during these tasks were in the dorsolateral prefrontal cortex, medial prefrontal cortex (including the anterior cingulate cortex), and the posterior parietal cortex (Nee et al., 2007; Swick et al., 2011). Thus, a fronto-parietal network appears to be important in supporting inhibitory control.

The typical clinical presentation of AD involves an early and prominent deficit in episodic memory, though the presence of a deficit in at least one other cognitive domain is necessary for the diagnosis of probable AD (McKhann et al., 2011). MCI is a term used to describe individuals who demonstrate an objective cognitive deficit but maintain preserved functional abilities, and thus do not meet diagnostic criteria for dementia (Albert et al., 2011). In many cases, MCI represents a prodromal phase of AD or other forms of dementia (Petersen et al., 2014), and therefore this is an important group to study in order to identify early cognitive and neuropathological changes that occur during the course of dementia. Depending on the presence or absence of an episodic memory deficit, MCI patients can be classified as either amnestic (aMCI) or non-amnestic (naMCI), with further specification given as to whether only one cognitive domain is affected (single domain) or multiple deficits are present (multiple domain). MCI patients who later develop AD most commonly present with an impairment in episodic memory, though other cognitive domains may also be impaired (Albert et al., 2011). Thus, these patients are either aMCI-single domain or aMCI-multiple domain.

AD patients are impaired on many components of executive functioning, and deficits on these tasks can be observed early in the course of the disease (Perry & Hodges, 1999; Weintraub et al., 2012). Longitudinal studies have shown that individuals who go on to develop AD show executive deficits even during the preclinical phase (e.g., Albert et al., 2007; P. Chen et al., 2001; Perri et al., 2007). Furthermore, a meta-analysis of studies that examined preclinical AD found that the effect size for executive dysfunction (d = 1.07) was approximately equal to the effect size for the episodic memory deficit (d = 1.03) (Bäckman et al., 2005). With regards to MCI patients, it has become increasingly clear that impairment in multiple cognitive domains is common (Bäckman et al., 2004; Loewenstein et al., 2006; Nordlund et al., 2005), and that progression to dementia is much more common in individuals with multiple deficits (Alexopoulos et al., 2006; Aretouli et al., 2013; Bozoki et al., 2001; Loewenstein et al., 2009). Executive functions appear to be a domain that is frequently impaired in MCI; however, findings from previous studies examining executive functioning in MCI are mixed (Johns et al., 2012).

There is some evidence that deficits in inhibition may be particularly prominent in MCI patients and AD patients (Amieva et al., 2004; Belleville et al., 2007; Johns et al., 2012). For example, Johns et al. (2012) examined multiple subcomponents of executive function in aMCI and found that executive dysfunction was present in all of the patients (z-scores of greater than

1.0 SD below the mean of controls on one or more measure), and that inhibitory control was the domain most frequently and severely impaired, with over 90% of patients demonstrating impairment on the Hayling Test. However, several studies have also reported no deficit on measures of inhibition (e.g., Bisiacchi et al., 2008; Lopez et al., 2006; D. Zheng et al., 2012; for a review, see Johns et al., 2012). However, despite the inconsistencies in the literature, it is clear that executive dysfunction can be detected in early AD, preclinical AD, and MCI.

The neural correlates of executive dysfunction in AD and MCI remain unclear. Though the neuropathology of AD is widespread and encompasses most brain areas in the later stages, atrophy of the frontal lobes is not typical of early and preclinical AD (Whitwell, Przybelski, et al., 2007b). Recent studies have demonstrated that amyloid deposition is present in the frontal lobes in the early stages of AD (Berti et al., 2010; Masdeu et al., 2012); however, amyloid pathology has not shown a consistent relationship with cognition (Wahlster et al., 2013). The current prevailing view is that disruption of neuronal networks likely plays an important role in executive dysfunction in AD and MCI (e.g., Bokde et al., 2009; Delbeuck et al., 2003; D. P. Salmon & Bondi, 2009).

There is mounting evidence for altered functional brain connectivity in AD and MCI. For example, resting state functional magnetic resonance imaging (rs-fMRI) studies have found altered connectivity in the default mode network in both AD and MCI patients (Filippi & Agosta, 2011). Furthermore, decreased rs-fMRI fronto-parietal functional connectivity has been observed in AD patients (Agosta et al., 2012; Dhanjal & Wise, 2014; K. Wang et al., 2007; Z. Wang et al., 2013), whereas increased connectivity has been reported within frontal networks (Agosta et al., 2012; Balachandar et al., 2014; K. Wang et al., 2007; L. Wang et al., 2006; H.-Y. Zhang et al., 2009; J. Zhou et al., 2010). There has been limited research on rs-fMRI connectivity in MCI patients for the frontal and fronto-parietal networks; however, some studies have reported increased frontal connectivity, similar to what has been observed in AD (Bai et al., 2009; Liang et al., 2011; Z. Qi et al., 2010; however, see Agosta et al., 2012 & Sorg et al., 2007), and one study reported no difference between MCI patients and controls in fronto-parietal connectivity (Agosta et al., 2012).

Functional connectivity can also be examined with electroencephalogram (EEG) or magnetoencephalogram (MEG) coherence or synchronization measures, which have a much higher temporal resolution than fMRI measures (though a lower spatial resolution for EEG).

EEG is used to record neuro-electrical brain activity at the scalp, and the resulting oscillatory activity can be spectrally decomposed in order to examine the relative power (magnitude) of the signal at each frequency band. Frequency bands commonly examined include delta (0.5-3.5 Hz), theta (3.5-7.5 Hz), alpha (7.5-12.5 Hz), beta (7.5-30 Hz) and low gamma (30-60 Hz). The spectrally decomposed data can also be used to calculate EEG coherence, which is a measure of the consistency of the relationship between the brain oscillations recorded at two electrode sites, and is a reflection of functional interaction between brain regions (Nunez et al., 1997). Coherence is sensitive to both magnitude and phase angle; though it is most strongly influenced by phase (Nunez & Srinivasan, 2006; Srinivasan et al., 2007). Other methods can also be used to examine synchronization between brain regions, including synchronization likelihood (a measure of both linear and non-linear relationships between the two channels), and phase coherence or synchronization.

3.2.1 Spontaneous EEG Coherence in AD and MCI

Many studies have examined resting state EEG coherence or synchronization in AD, and the most common finding is a widespread reduction in alpha and beta coherence (C. Babiloni et al., 2011; 2015). Findings for resting state EEG coherence in the delta, theta, and gamma frequency bands have been more variable, with some studies reporting decreased coherence in the lower frequency bands (e.g., Adler et al., 2003; C. Babiloni, Ferri, et al., 2006b; Knott et al., 2000; Sankari et al., 2012), and others reporting no differences (e.g., Fonseca et al., 2013; Jelles et al., 2008; Ma et al., 2014; Stam et al., 2005). Fewer studies have examined the gamma band, and results have been variable here as well (e.g., C. Babiloni, Ferri, et al., 2004b; 2006b; Jelles et al., 2008; Koenig et al., 2005; Ma et al., 2014; Stam et al., 2005; Tao & Tian, 2005).

In contrast to the findings in AD patients, studies of resting state coherence in MCI patients have found decreased coherence specifically between frontal and posterior regions across frequency bands (C. Babiloni, Ferri, et al., 2006b; Moretti et al., 2008; Tóth et al., 2014; Xu et al., 2014; however, see Tao & Tian, 2005). Typically, MCI patients do not show reduced coherence for interhemispheric frontal, temporal, and parietal electrode pairs nor for local intrahemispheric pairs (C. Babiloni, Ferri, et al., 2006b; Jiang et al., 2008; Moretti et al., 2008; Tao & Tian, 2005; Teipel et al., 2009). Thus, changes in fronto-posterior connectivity may be an early sign of AD.

3.2.2 Event-related EEG Coherence in AD and MCI

Studies of resting state EEG coherence provide valuable insight into functional brain changes while at rest; however, additional or different changes in brain functioning could be present as a result of cognitive task demands. Few studies have examined EEG coherence during the performance of cognitive tasks in MCI and AD; however, generally speaking, coherence is increased during the performance of a cognitive task in comparison to control tasks (Başar et al., 2010). Furthermore, decreased coherence in AD patients in comparison to normal controls has been found to be more widespread (i.e., involving more electrode pairs and frequency bands) during the performance of a cognitive task than during control tasks (Başar et al., 2010; Tao & Tian, 2005). Coherence has been examined in AD patients during the performance of sustained attention (visual oddball) and short-term memory tasks. During sustained attention tasks, decreased coherence has been found between frontal and posterior areas in the lower frequency bands (delta, theta, alpha) (Başar et al., 2010; Güntekin et al., 2008). For short-term memory tasks, averaged synchronization likelihood has been reported to be decreased in AD patients in the alpha and beta bands (Pijnenburg et al., 2004), and centro-temporal coherence has been reported to be decreased in the alpha band (Hogan et al., 2003). In addition, Pijnenburg et al. (2004) found that better performance on a short-term memory task was associated with lower delta synchronization and higher alpha synchronization during task performance. To our knowledge, there are no studies to date that have examined EEG coherence during the performance of an executive functioning task in AD patients.

In MCI patients, event-related coherence or synchronization has been examined during short-term memory tasks (Bajo et al., 2010; Pijnenburg et al., 2004), target counting (Tao & Tian, 2005), and in one set of studies, a working memory (mental addition) task (Jiang, 2005b; Jiang et al., 2008; L.-L. Zheng et al., 2007). In the study that examined target detection, only the gamma band was examined, and MCI patients exhibited reduced fronto-temporal and fronto-central coherence during the performance of the task (fronto-parietal coherence was not examined) (Tao & Tian, 2005). In the two studies that examined synchronization likelihood during the performance of short-term memory tasks, overall synchronization was increased in the alpha band (Pijnenburg et al., 2004), and increased synchronization was also observed for interhemispheric anterior regions in the alpha and beta band and for anterior and posterior regions in the gamma band (Bajo et al., 2010). In contrast, decreased synchronization was

found for intrahemispheric temporal and central regions in the alpha and beta bands and for intrahemispheric temporal, central, central-posterior, and fronto-posterior regions in the gamma band. In the only set of studies to examine EEG coherence during a task of executive functioning in MCI patients, there was a widespread increase in coherence across all frequency bands during the working memory task for MCI patients in comparison to controls (Jiang, 2005b; Jiang et al., 2008; L.-L. Zheng et al., 2007).

Thus, the existing research suggests that MCI patients exhibit a widespread increase in both interhemispheric and long distance intrahemispheric coherence during task performance (though decreased fronto-posterior gamma coherence has also been reported during task performance). This increase in coherence during task performance is hypothesized to represent a compensatory mechanism in which MCI patients must recruit additional neural resources when performing cognitive functions, possibly in order to compensate for inefficient antero-posterior connections (Bajo et al., 2010; Jiang et al., 2008).

3.2.3 The Present Study

Given the evidence of impaired inhibitory control in MCI and AD and the lack of a clear understanding of the neural underpinnings of this deficit, the primary goal of the present study was to examine the relationship between EEG coherence and inhibitory control in MCI, AD, and normal elderly controls. Therefore, we examined EEG coherence during the performance of a Go/No-go task of inhibitory control. We examined electrode pairs within a fronto-parietal network, as previous research has found these areas to be activated during the performance of inhibitory control tasks (Nee et al., 2007; Swick et al., 2011), and increased fronto-parietal EEG coherence has been implicated in tasks of inhibition (Brier et al., 2010; Qassim et al., 2013). In this study, we examined the same participants as in two concurrent studies, in order to allow for direct comparison across studies. One of these studies examined EEG coherence at rest (Johns, Nikelski, Soucy, Chertkow, & Phillips, 2015), and the other examined EEG coherence during the performance of a working memory task (Johns & Phillips, 2015b). This enabled us to examine the relationship between EEG coherence during the performance of the Go/No-go task and measures of neuropathology (cortical thickness and PiB retention) presented in Johns et al. (2015).

We first examined group differences for Go/No-go task performance and EEG coherence and then conducted several exploratory correlations in order to investigate the relationships

between EEG coherence during task performance and neuropathology (cortical thickness and PiB retention) as well as cognitive performance on the Go/No-go task. Based on the previous literature, we predicted decreased reaction time on the Go/No-go task for both AD and MCI patients, but no differences in accuracy (Amieva et al., 2002; Collette et al., 2007; Zihl et al., 2010). With regards to EEG coherence, based on previous studies that have examined event-related coherence in AD and MCI (reviewed above), we predicted that AD patients would exhibit decreased fronto-parietal coherence in the lower frequency bands, and that this effect would be larger for No-go trials than for Go trials, as No-go trials require inhibitory control and Go trials do not. For MCI patients, we predicted increased coherence for both interhemispheric (frontal and parietal) and intrahemispheric (fronto-parietal) pairs, and that this effect would be greater for No-go trials. With respect to the inter-correlations, due to the limited amount of previous literature in this area, we did not make any specific predictions, but rather treated the correlations as exploratory in nature.

3.3 Methods

3.3.1 Participants

Twenty-one MCI patients, 16 AD patients, and 26 normal elderly controls (NECs) were selected for inclusion in the final sample of the present study. The same participants used in two of our concurrent studies (Johns et al., 2015; Johns & Phillips, 2015b) were selected for this study in order to allow for direct comparison across studies. A general health questionnaire was administered to screen participants for neurological conditions other than MCI or AD, medical conditions that might affect cognition (e.g., uncontrolled thyroid dysfunction, B_{12} deficiency, alcohol abuse), and psychiatric disorders (other than mild depression). In addition, the Geriatric Depression Scale (GDS; Yesavage et al., 1982) was administered, and any participant with a score greater than six was not admitted to this study. The Subjective Memory Complaints Scale (SMCS; Schmand et al., 1996) was also administered in order to characterize self-ratings of memory functioning. From the larger sample initially recruited for this study, two MCI patients, one AD patient, and seven NECs were excluded in order to generate a sample with identical participants to those used in the analysis of data collected for our concurrent studies (Johns et al., 2015; Johns & Phillips, 2015b). Reasons for exclusion included insufficient artifact-free epochs in any of the conditions, atypical task performance, technical errors during testing, or excessively noisy EEG recordings.

As reported elsewhere (Johns et al., 2015), MCI and AD participants were recruited and diagnosed at the Memory Clinic of the Sir Mortimer B. Davis–Jewish General Hospital (JGH), a tertiary care referral center of McGill University, Montreal. Their clinical evaluations included full medical, neuropsychological, and neuroradiological assessments. NECs were recruited from research participation databases at the Cognition, Aging, and Psychophysiology Laboratory at Concordia University and the Memory Clinic at the JGH. Written informed consent was obtained from all participants, who were compensated $10 per hour for their participation. Participants were tested at Concordia University and the Jewish General Hospital, and ethical approval for the study was obtained from both institutions involved.

3.3.1.1 MCI patients. A diagnosis of MCI was given based on agreed-upon criteria (Petersen et al., 2009; Winblad et al., 2004), which included a subjective report of cognitive decline (by either the individual or family), which was gradual and of at least 6 months duration, a documentation of objective cognitive impairment on neuropsychological testing (i.e., ±1.5 SD of age-appropriate norms), the absence of significant impairment in activities of daily living, and failure to meet the ADRDA-NINCDS criteria for dementia (McKhann et al., 1984), as determined by the assessing physician in the Memory Clinic. All MCI patients were amnestic, either demonstrating an impairment on measures of episodic memory alone or impairments in episodic memory plus other cognitive domains.

3.3.1.2 AD patients. A diagnosis of AD was given based on the ADRDA-NINCDS criteria for possible or probable AD (McKhann et al., 1984), which included an established progressive cognitive decline and the absence of any other disease capable of producing the dementia syndrome. Only participants who were deemed to be able to sign the consent form without assistance were included in this study; thus, all AD patients had a mild to moderate level of cognitive impairment and no severe cases were included (average MoCA score = 19.3).

3.3.1.3 Normal elderly controls. NECs were screened for general cognitive function using the Montreal Cognitive Assessment (MoCA; Nasreddine et al., 2005), a cognitive screening tool that is sensitive to detecting MCI. NECs were excluded if they scored below 26 on this measure.

3.3.2 Materials and Procedure

All participants completed a neuropsychological testing session and an EEG testing session, and subset of participants also completed MRI and PiB scans. EEG was recorded while

at rest (data presented in Johns et al., submitted), during the Go/No-go task, and during two other executive functioning tasks (data not presented here). The procedures for the neuropsychological testing and neuroimaging acquisition and processing were identical to those reported by (Johns et al., 2015), and are presented below.

3.3.2.1 Neuropsychological Testing. All participants completed a neuropsychological test battery administered according to standardized procedures and in a standardized order. The battery included measures of verbal abstract reasoning (Similarities subtest of the Wechsler Adult Intelligence Scale-Third Edition, WAIS-III; Wechsler, 1997), processing speed (Symbol Search subtest of the WAIS-III; Wechsler, 1997), short-term memory span (Digit Span subtest of the WAIS-III; Wechsler, 1997), confrontational naming (Boston Naming Test, 15-item version; Kaplan et al., 1983), verbal episodic memory (California Verbal Learning Test – Second Edition; Delis et al., 2000), working memory (Letter Number Sequencing subtest of the WAIS-III; Wechsler, 1997), phonemic and semantic verbal fluency (letters F, A, and S, and animals; Strauss et al., 2006), cognitive flexibility (Trail Making Test; Reitan, 1979; Strauss et al., 2006), and inhibitory control (Hayling Sentence Completion Test; Burgess & Shallice, 1997; and Victoria verion of the Stroop Test; Strauss et al., 2006).

3.3.2.2 EEG Recording. EEG was recorded during the performance of the Go/No-go task, as well as while at rest (eyes-closed) for three minutes and during the performance of two other executive function tasks (data not presented here). The data were acquired using Neuroscan Acquire software (Neuroscan, 2003) from 32 Ag/AgCl electrodes mounted in an elastic Easycap and placed according to the International 10-20 system, with a bandpass of DC-100 Hz and a sampling rate of 500 Hz. All sites were referenced to the left ear and re-referenced offline to linked ears. Electrode impedances were kept below 8 kΩ (and in most cases, below 5 kΩ). Electro-oculogram (EOG) activity was recorded supra-orbitally and from the outer canthi of both eyes in order to monitor eye movement, and corrected offline using ocular correction independent component analysis in BrainVision Analyzer 2.0 (*BrainVision Analyzer User Manual*, 2013).

3.3.2.3 Spectral analysis of EEG data. EEG data were processed offline using BrainVision Analyzer 2.0 software (*BrainVision Analyzer User Manual*, 2013). A DC drift correction and a 1-50 Hz phase shift-free Butterworth filter with a 12 db roll-off was applied to the continuous EEG files. EEG recorded during the Go/No-go task was segmented in 1024 ms

epochs beginning at the presentation of the stimulus for each trial. Segments containing deflections of greater than ±100 μV were excluded from further analysis. Data were transformed to the frequency domain using a fast Fourier transform (FFT) with a Hanning window. Average power and coherence were calculated for the following frequency bands: delta (1-3.5 Hz), theta (3.5-7.5 Hz), alpha (7.5-12.5 Hz), beta (12.5-30 Hz), and gamma (30-45 Hz).

3.3.2.4 Spectral Coherence Analysis. EEG coherence was calculated using the following formula for segment number i, fixed frequency f, and fixed channel c:

$Coh(c_1, c_2)(f) = | CS(c_1, c_2)(f) |^2 / (| CS(c_1, c_1)(f) | | CS(c_2, c_2)(f) |)$,

where $CS(c_1, c_2)(f) = \Sigma\, c_{1,\,i}\,(f)\, c_{2,\,i}\,(f)$

The numerator contains the cross-spectrum of two EEG signals c_1 and c_2 ($CS(c_1, c_2)$) for a given frequency bin (f) and the denominator contains the autospectra for c_1 ($CS(c_1, c_1)$) and c_2 ($CS(c_2, c_2)$). The coherence value is equivalent to the squared complex correlation coefficient (Pfurtscheller & Andrew, 1999; Rappelsberger & Petsche, 1988), and coherence values range from 0 (no coherence) to 1 (maximal coherence). EEG coherence was computed for the following electrode pairs of interest: F3-F4, P3-P4, O1-O2, F3-P3, and F3-O1. These electrode pairs were chosen based on previous research that has implicated a fronto-parietal network underlying executive function, and the cross-hemisphere occipital pair and fronto-occipital pair were chosen for comparison to electrode pairs outside the fronto-parietal network. For the calculation of EEG coherence, the minimum number of segments was 189 for Go trials (M = 438) and 20 for No-go trials (M = 57). A Fisher's Z transformation was applied to the square root of coherence values in order to normalize the distribution for statistical analysis.

3.3.2.5 MRI acquisition & cortical thickness processing. Cortical thickness data were available for seven NECs, 17 MCI patients, and seven AD patients. MRI scans were acquired on a 1.5 Tesla Siemens Sonata Vision scanner at the Montreal Neurological Institute (MNI) and were done within one year of the EEG testing for MCI patients (M = 0.56 years) and within two years of EEG testing for NECs (M = 1.10 years) and AD patients (M = 1.21 years). High-resolution T1-weighted anatomical scans were obtained using a three-dimensional spoiled gradient echo sequence (T_R= 22ms; T_E= 9.2ms; flip angle= 30°; FOV = 256 x 256; 160 or 176 slices; 1-mm isotropic) along the sagittal plane.

MRI scans were processed using the automated CIVET pipeline (The McConnell Brain Imaging Centre, Montreal Neurological Institute). Briefly, tissue classification generated a gray

and white matter surface for each subject, which was then aligned to a model surface. The difference in distance between the aligned gray and white matter surfaces was computed at each of 81924 vertices (40962 per hemisphere) using the *t-link* method, providing a measure (in mm) of cortical thickness at each of those vertices. Finally, thickness values were smoothed using a 20-mm surface smoothing filter. In order to permit analysis by region of interest (ROI), customized Automated Anatomical Labeling atlas (Tzourio-Mazoyer et al., 2002) labels were strongly warped (non-linearly) onto the subject's surface, yielding an individually-labeled surface with one label at each vertex. Next, the thickness vector file was matched against the newly created labels vector file, allowing for the computation of cortical thickness values for each ROI. The ROIs analyzed in the present study were chosen to sample frontal and parietal areas as a comparison for the EEG data as well as medial temporal areas, which are known to be affected in early AD. The five ROIs selected were the superior frontal gyrus, middle frontal gyrus, anterior cingulate cortex, superior parietal lobule, and parahippocampal gyrus (all in the left hemisphere).

3.3.2.6 PiB-PET acquisition and processing. PiB-PET data were available for 10 NECs, 13 MCI patients, and seven AD patients. Scans were acquired on a Siemens/CTI ECAT HR+ scanner in 3-dimensional imaging mode (63 parallel planes) at the MNI. All scans were done within one year of the EEG testing for MCI patients (M = 0.57 years) and within two years of EEG testing for NECs (M = 0.87 years) and AD patients (M = 1.08 years). Subjects were scanned either for either 90 minutes immediately following injection of the [C-11]PiB bolus (34 frames collected) or for 40 minutes commencing 50 minutes after the injection (7 frames collected). The difference in scanning times was due to a need to shorten scan times after receiving feedback from participants that the scan time was too long.

The PiB volume was aligned to the participants' native anatomy according to the T1-weighted MRI scan. This was followed by registration of both native-space volumes to the MNI symmetrical template using a 12-parameter linear transformation. The resulting stereotactic-space dynamic volume was blurred with a 6-mmm full-width at half-maximum Gaussian filter in order to minimize the effects of random high-frequency spikes in the data and increase the signal-to-noise ratio. Blurring filter width was minimized in order to prevent the blurring of the signal within the cerebellar gray and white matter.

Ratio values were computed at each voxel using all seven frames collected during 40 minute scans and the last five frames collected during 90 minute scans (50 minutes post-injection, 40 minutes total scan time). First, the area under the curve (AUC) across time was computed for the cerebellar gray matter reference values, and at each voxel within the volume. Ratios were then computed by dividing each voxel's AUC value by the cerebellar gray AUC. Average PiB ratio values were computed for each ROI as defined by the Automated Anatomical Labeling atlas (Tzourio-Mazoyer et al., 2002). Consistent with the cortical region ROIs, the six ROIs that were analyzed in the present study were the superior frontal gyrus, middle frontal gyrus, anterior cingulate cortex, superior parietal lobule, hippocampus, and parahippocampal gyrus (all in the left hemisphere).

3.3.2.7 Go/No-go task. The Go/No-go task is a response inhibition task in which participants must inhibit a prepotent response (button press) on infrequent trials. The letters b, d, p, and q were presented sequentially on a computer screen in a pseudorandomized order in white font on a black background (Arial 150 point font). Each letter was presented for a duration of 150 ms with an inter-stimulus interval of 1000 ms. Pseudorandomization was used to ensure no more than two consecutive No-go trials and no more than 13 consecutive Go trials. One of the letters was designated as the No-go letter (counterbalanced across participants), which was presented on 15% of trials. On these No-go trials, participants were to inhibit the response of a button press and they were asked to press the button as quickly as possible in response to the remaining three letters (Go trials). The task was presented in six blocks of 50 trials at the beginning of the testing session and six at the end of the session (the task was divided into blocks in order to avoid fatigue). Additional blocks were presented as needed until each participant reached a minimum of 20 errors on No-go trials. The mean number of trials was 633 for NECs, 626 for MCI patients, and 634 for AD patients. Participants were asked to respond as quickly and accurately as possible using the index finger of the preferred hand (92% of NECs, 90% of MCI patients, and 94% of AD patients were right handed). Trials in which responses occurred in less than 150 ms following the stimulus presentation or greater than 3 standard deviations longer than the participant's mean reaction time were excluded.

3.4 Results

Data for demographic characteristics, neuropsychological testing, cortical thickness, and PiB retention have been presented elsewhere (Johns et al., 2015), and are summarized in Table

3.1. Briefly, there were no significant differences between groups in age, educational level, sex distribution, or depressive symptomatology. AD patients reported higher subjective memory complaints (SMCS) than NECs, and there was a trend for higher subjective memory complaints in MCI patients versus NECs. On the MoCA test, both AD patients and MCI patients scored lower than NECs, and AD patients also scored lower than MCI patients.

Neuropsychological testing was conducted in order to characterize the groups and verify the presence of deficits in executive functioning. Each neuropsychological test was analyzed with a separate univariate or multivariate analysis of variance (ANOVA), as appropriate. AD patients performed significantly worse than controls on a number of measures across several cognitive domains. These included verbal abstract reasoning (Similarities subtest), visual processing speed (Symbol Search), Digit Span forward, confrontational naming (Boston Naming Test), verbal episodic memory (CVLT total learning trials and delayed recall), working memory (Letter-Number Sequencing subtest), semantic and phonemic verbal fluency, and inhibitory control (errors on the Stroop test and errors on the Hayling test). MCI patients also performed significantly worse than controls on a number of measures, including verbal abstract reasoning (Similarities subtest), visual processing speed (Symbol Search), verbal episodic memory (CVLT total learning trials and delayed recall), semantic verbal fluency, and inhibitory control (Hayling test errors).

Cortical thickness and PiB retention were analyzed using separate multivariate ANOVAs. Cortical thickness was reduced in the parahippocampal gyrus in MCI and AD patients in comparison to controls and in the anterior cingulate cortex in AD patients (with a non-significant trend for reduced thickness in MCI patients). PiB retention was higher in AD patients in comparison to controls in the superior frontal gyrus, middle frontal gyrus, anterior cingulate cortex, and superior parietal lobule. In MCI patients, PiB retention was higher than that of controls in the superior frontal gyrus, and there were non-significant trends for higher PiB retention in the middle frontal gyrus and the anterior cingulate cortex.

3.4.1 Statistical Analysis

Statistical analysis was conducted using SPSS v.22.0 software. For analyses with more than one degree of freedom in the numerator, a Huynh and Feldt (1976) correction was used for violations of sphericity. In these cases, the unadjusted degrees of freedom, the adjusted *p*-value, and the Huynh-Feldt epsilon value (ε) are reported.

3.4.2 Go/No-go Behavioural Results

Reaction time for Go trials and accuracy (% correct) for No-go trials were analyzed with separate univariate ANOVAs. As shown in Figure 3.1, the groups differed reliably for reaction time, $F(2, 60) = 6.37$, $p = .003$, $\eta^2_p = .16$, with AD and MCI patients responding slower than NECs ($p = .002$ and $p = .013$, respectively), but not differing significantly from one another. There were no group differences for accuracy. All three groups performed at ceiling levels for accuracy on Go trials (NEC: 100%, MCI: 100%, AD: 99.3%).

3.4.3 Spectral EEG Power Analysis

Average power for each frequency band was measured for frontal (F3, Fz, F4), central (C3, Cz, C4), parietal (P3, Pz, P4), and occipital (O1, O2) electrode sites. The data were positively skewed; therefore, a logarithmic transformation was applied in order to normalize the distributions.

Mean power during Go and No-go trials is presented in Figure 3.2. A 5 x 4 x 2 x 3 mixed design ANOVA was used to analyze spectral power for the Go/No-go task in order to examine the effects of frequency band (delta, theta, alpha, beta, gamma), electrode site (frontal, central, parietal, occipital), trial type (Go, No-go), and group (NEC, MCI, AD). There were no main effects of trial type, $F(1, 61) = 0.44$, $p = .509$, $\eta^2_p = .01$, or group, $F(2, 61) = 1.48$, $p = .236$, $\eta^2_p = .05$. There was a main effect of frequency band, $F(4, 244) = 417.43$, $p < .001$, $\eta^2_p = 0.87$, $\varepsilon = .578$, such that power was greatest in the delta band followed by theta, alpha, beta, and gamma ($p < .05$ in all cases).

The interaction between frequency band, trial type, site, and group was marginally significant, $F(24, 732) = 1.78$, $p = .065$, $\eta^2_p = 0.06$, $\varepsilon = .415$. We conducted planned pairwise comparisons to examine the effects of trial type and group (effects reported as significant are all $p < .05$).

3.4.3.1 Effect of trial type. In the delta band, power was increased for No-go trials relative to Go trials at frontal, central, and parietal sites for all three groups. Interestingly, in the theta band, the effect of trial type was observed only for NECs, in which theta power was increased for No-go trials relative to Go trials at frontal and central sites, but decreased at occipital sites. In the alpha band, power was greater for Go trials in comparison to No-go trials for all sites and groups. In the beta band, power was greater for Go trials in comparison to No-go trials for MCI patients and NECs at parietal and occipital sites, and for MCI patients only at

frontal and central sites. Finally, in the gamma band, power was greater for Go trials in comparison to No-go trials for MCI patients and NECs at occipital sites, for NECs only at parietal sites (non-significant trend in the same direction for MCI patients) and for MCI patients only at frontal sites.

3.4.3.2 Effect of group.

3.4.3.2.1 AD patients versus NECs. In the delta band, central power for No-go trials was reduced in AD patients in comparison to NECs. There were no group differences in the theta band. In the alpha band, occipital power was reduced for both Go and No-go trials, and in the beta band, parietal and occipital power were reduced for both Go and No-go trials and frontal power was reduced for Go trials. No group differences were observed for the gamma band.

3.4.3.2.2 MCI patients versus NECs. In the delta band, occipital power was decreased for No-go trials. In the theta and alpha bands, occipital power was decreased for both Go and No-go trials. There were no group differences for the beta and gamma bands.

Overall, this pattern of results indicates that, in NECs, power in the lower frequency bands is greater for No-go trials, which involve more controlled cognitive processing, than for Go trials, which involve more automatic cognitive processing. This pattern is most prominent at frontal and central sites. In contrast, power in the higher frequency bands is more prominent for Go trials in comparison to No-go trials, and this pattern is particularly evident at posterior electrode sites. AD patients showed the same effect of trial type as NECs only for the delta and alpha bands. MCI patients showed the same effect of trial type as NECs for the delta, alpha, beta, and gamma bands, with the additional effect of trial type (Go>No-go) at frontal and central sites in the beta band and at frontal sites in the gamma band.

Power was reduced for AD patients relative to controls in the delta (central for No-go trials), alpha (occipital for both Go and No-go trials), and beta bands (parietal and occipital for both Go and No-go trials and frontal for Go trials), and power was reduced for MCI patients relative to controls in the delta (No-go trials), theta (Go and No-go trials), and alpha (Go and No-go trials) bands.

3.4.4 EEG Coherence

The analysis of EEG coherence was performed separately for each frequency band and family of electrode pairs (cross-hemisphere homologous pairs and long distance intrahemispheric pairs). The family of cross-hemisphere homologous pairs was analyzed using 3 x 2 x 3 mixed

design ANOVAs to examine the effects of electrode pair (F3-F4, P3-P4, O1-O2), trial type (Go, No-go) and group (NEC, MCI, AD), and the family of long distance intrahemispheric pairs was analyzed using 2 x 2 x 3 mixed design ANOVAs to examine the effects of electrode pair (F3-P3, F3-O1), trial type (Go, No-go) and group (NEC, MCI, AD).

3.4.4.1 Cross-hemisphere homologous pairs. The statistics for the significant main effects and interactions for cross-hemisphere homologous pairs are presented in Table 3.2.

3.4.4.1.1 Effect of trial type. One critical goal of this paper is to understand how EEG coherence changes as a function of inhibitory control demands. Thus, for these analyses, we focus on the contrast between Go and No-go trials and whether the pattern differs in patients compared to controls. As can be seen in Table 3.2, there were main effects of trial type for all frequency bands, and interactions between trial type and electrode pair in the delta, theta, beta, and gamma bands. Follow-up comparisons revealed that coherence was higher for No-go (inhibition) trials than for Go trials for all electrode pairs except the occipital pair in the delta and gamma bands. In addition, in the delta band, the effects of trial type (i.e., increased coherence for No-go trials compared to Go trials) for F3-F4 and P3-P4 were greater than for O1-O2, and in the theta, beta, and gamma bands, the effect of trial type was greater for F3-F4 in comparison to both P3-P4 and O1-O2. This greater increase in coherence for inhibition trials for the frontal pair in comparison to posterior pairs suggests that the frontal "executive" component of this task may be best reflected by the activity in the theta, beta, and gamma bands.

3.4.4.1.2 Group differences. As shown in Table 3.2, group differences in EEG coherence during the Go/No-go task were observed only for the theta band. There was a main effect of group in which AD patients had overall lower coherence than both MCI patients (p = .004) and controls (p = .023). There was also a significant electrode pair x trial type x group interaction (see Figure 3.3, top panel). Pairwise comparisons revealed the following: (1) for F3-F4, there were trends for AD<MCI for Go trials (p = .080), and for AD<MCI=NEC for No-go trials (p = .056 for AD vs. MCI and p = .057 for AD vs. NEC); (2) for P3-P4, AD patients had lower coherence than both MCI patients and controls for both Go trials (p = .001 and p = .015, respectively) and No-go trials (p = .013 and p = .053, respectively); (3) for O1-O2, there were no differences between groups. This suggests that AD patients show a deficit in cross-hemisphere frontal coherence in comparison to normal controls specifically during inhibition trials and a deficit in cross-hemisphere parietal coherence during the whole task.

In order to further explore this effect, we examined the difference scores for coherence during No-go trials versus coherence during Go trials (Figure 3.4). Thus, values greater than zero indicate an increase in coherence on No-go trials versus Go trials. There was a significant electrode pair x trial type x group interaction, $F(4, 120) = 2.84$, $p = .035$, $\eta^2_p = 0.09$, $\varepsilon = .862$, in which normal controls exhibited a greater increase in coherence between trial type than both MCI patients ($p = .017$) and AD patients ($p = .007$) for the cross-hemisphere frontal electrode pair (F3-F4), but not the posterior pairs (P3-P4 and O1-O2). Thus, while mean cross-hemisphere frontal coherence values do not differ reliably between MCI patients and normal controls for either Go or No-go trials, MCI patients show a smaller increase in coherence for No-go trials in comparison to Go trials. In fact, though MCI patients show overall higher frontal coherence in comparison to AD patients (see Figure 3.3, top left panel), the difference in coherence for No-go versus Go trials is the same in both patient groups, and is reduced in comparison to normal controls.

3.4.4.2 Long distance intrahemispheric pairs. The statistics for the significant main effects and interactions intrahemispheric pairs are presented in Table 3.3.

3.4.4.2.1 Effect of trial type. There were main effects of trial type and interactions between trial type and electrode pair for all frequency bands. Follow-up comparisons revealed that coherence was higher for No-go (inhibition) trials than for Go trials for both F3-P3 and F3-O1 in all frequency bands ($p < .001$ in all cases). Furthermore, the effect of trial type (i.e., increased coherence for No-go trials compared to Go trials) was greater for F3-P3 than for F3-O1 for the delta and theta bands (see Figure 3.3, bottom panel for a depiction of the effect of trial type in the theta band). In contrast, the reverse pattern was observed for the alpha, beta, and gamma bands, in which the effect of trial type was greater for F3-O1 (see Figure 3.5 for a depiction of the effect of trial type in the alpha band).

3.4.4.2.2 Group differences. As shown in Table 3.3, there were no main effects of group; however there were non-significant trends for trial type x group interactions in the alpha and beta bands. Follow-up comparisons for the alpha band revealed that MCI patients exhibited higher coherence than controls for No-go trials ($p < .05$) and a trend towards higher coherence than AD patients for No-go trials ($p = .075$). MCI patients also exhibited a greater effect of trial type (No-go>Go) than AD patients ($p < .05$), and a non-significant trend in the same direction in comparison to controls ($p = .078$; see Figure 3.5). Follow-up comparisons for the beta band

revealed no reliable group differences for either Go or No-go trials, and a greater effect of trial type (No-go>Go) for AD patients in comparison to MCI patients. There were no group differences in the effect of trial type for either patient group in comparison to normal controls. Thus, MCI patients appear to have an increased effect of trial type in the alpha band for long-distance intrahemispheric pairs.

3.4.5 Correlational Analysis

We computed several exploratory Pearson correlations in order to examine the relationship between the various neuroimaging measures and between the neuroimaging measures and measures of cognitive performance. We examined EEG coherence for the difference between No-go and Go trials (a larger difference indicating a greater increase in coherence for No-go trials in comparison to Go trials) for electrode pairs of interest (F3-F4, P3-P4, F3-P3) for all frequency bands. We ran two sets of correlational analyses: (1) intercorrelations between neuroimaging measures for ROIs within frontal and parietal areas, and (2) correlations between neuroimaging measures and performance on the Go/No-go task. We consider these data to be exploratory in nature due to the large number of correlations computed as well as the small sample size. As we were interested in exploring the relationship between these various measures in each of the individual groups, the sample size for the correlations is often quite small (e.g., $n = 7$ for any correlations with cortical thickness or PiB retention values for AD patients; refer to sample sizes presented in Table 3.1). Nevertheless, several significant correlations emerged in our examination of the data.

3.4.5.1 EEG coherence, cortical thickness, and PiB retention. First, we examined the relationship between EEG coherence (i.e., the difference between No-go and Go trials) and both cortical thickness and PiB retention. A summary of the significant correlations is presented in Table 3.4. From this table, it can be seen that there were overall fewer correlations for AD patients than for NECs and MCI patients. In addition, in normal controls, there were more correlations for EEG coherence and PiB retention than for EEG coherence and cortical thickness, and there was very little overlap across groups in significant correlations.

3.4.5.1.1 EEG coherence and cortical thickness. There was no consistent relationship between EEG coherence and cortical thickness in NECs (only a negative association between parietal delta coherence and thickness of the anterior cingulate cortex and a positive association between parietal theta coherence and thickness of the middle frontal gyrus). In contrast, there

was a consistent negative relationship between EEG coherence and cortical thickness in MCI patients, and a positive relationship between coherence and cortical thickness in AD patients. Thus, in MCI patients, lower cortical thickness in frontal and parietal regions was associated with a greater increase in cross-hemisphere coherence in the lower frequency bands (delta and theta) with inhibitory control demands. In contrast, in AD patients, lower cortical thickness in frontal regions is associated with less of an increase in cross-hemisphere parietal coherence in the theta and gamma bands.

3.4.5.1.2 EEG coherence and PiB retention. Table 3.4 shows a strikingly different pattern of correlations across the three groups with respect to which frequency bands are correlated with PiB retention and the direction of the relationships. In NECs, there were a number of reliable negative correlations with PiB retention for coherence in the gamma band. In contrast, only coherence in the beta band was reliably correlated in the two patient groups, with a positive relationship for the MCI patients and a negative relationship for the AD patients. Furthermore, in NECs, the correlations were primarily with the cross-hemisphere frontal electrode pair, whereas in MCI patients, the reliable correlations were seen only for the cross-hemisphere parietal electrode pair. Sample scatterplots for correlations between EEG coherence and PiB retention in the superior frontal gyrus for MCI patients and NECs are presented in Figure 3.6.

Thus, overall, increased amyloid burden in NECs and AD patients was associated with less of an increase in EEG coherence on inhibition trials during the Go/No-go task. In contrast, increased amyloid burden was associated with a greater coherence increase on inhibition trials in MCI patients. PiB retention was associated with coherence increase in cross-hemisphere frontal and parietal pairs for NECs, for cross-hemisphere parietal pairs only for MCI patients, and for cross-hemisphere frontal and intrahemispheric fronto-parietal pairs for AD patients.

3.4.5.2 Neuroimaging and Go/No-go performance. The relationship between neuroimaging measures (EEG coherence, cortical thickness, and PiB retention) and Go/No-go behavioural performance is presented in Table 3.4. There were few significant correlations between neuroimaging measures and behavioural performance, and the correlations that were significant were not consistent across groups. For NECs, there were no reliable associations between neuroimaging measures and Go/No-go performance. For MCI patients, lower cross-hemisphere parietal alpha coherence and lower fronto-parietal theta coherence were associated

with greater Go/No-go accuracy. Higher parietal alpha coherence and lower middle frontal gyrus cortical thickness were associated with faster reaction time on the Go/No-go task. For AD patients, lower parietal and fronto-parietal alpha coherence was associated with higher accuracy, and less PiB retention in the anterior cingulate cortex was associated with faster reaction time. Overall, these results are not indicative of a particularly consistent or robust relationship between any of the neuroimaging measures and performance on the Go/No-go task.

3.5 Discussion

The main goal of the present study was to examine the relationship between EEG coherence and inhibitory control in MCI and AD. We examined EEG coherence within a fronto-parietal network during the performance of a task of inhibitory control (Go/No-go task). We were also interested in exploring the relationship between EEG coherence, cognition, and measures of brain integrity (cortical thickness and PiB retention); therefore we conducted a number of exploratory correlations to examine these relationships. Results are summarized and discussed below.

3.5.1 Group Differences on Cognitive Measures

Neuropsychological testing was conducted in order to confirm the presence of deficits in executive functioning in MCI and AD patients. On measures of executive function, AD patients demonstrated deficits on measures of working memory, semantic and phonemic verbal fluency, and inhibitory control, and MCI patients exhibited deficits on tests of semantic verbal fluency and inhibitory control. In other domains of cognitive function, deficits were observed on measures of verbal abstract reasoning, visuomotor processing speed, short-term memory span, confrontational naming, and verbal episodic memory for AD patients, and on measures of verbal abstract reasoning, visual processing speed, and verbal episodic memory for MCI patients. With regards to neuropsychological measures of inhibition, AD patients produced more errors than controls on both the Stroop test and the Hayling Test, and MCI patients produced more errors on the Hayling test. The number of errors generated on the Hayling test was similar for AD patients and MCI patients, suggesting that semantic inhibition may be a subcomponent of executive functioning that is particularly sensitive to detecting deficits early in the course of the disease, and is consistent with previous research (Johns et al., 2012).

With regards to the Go/No-go task, our experimental measure of inhibitory control during which we recorded EEG, both AD and MCI patients had longer reaction times, but accuracy did not differ from that of normal controls.

3.5.2 EEG Coherence: Effect of Trial Type

With respect to EEG coherence during the Go/No-go task, we found a robust effect in which EEG coherence was modulated by the presence of inhibitory control demands. Specifically, EEG coherence was consistently higher for No-go trials in comparison to Go trials for all electrode pairs, frequency bands, and groups. Furthermore, for cross-hemisphere electrode pairs, the effect of increased coherence for inhibition trials was greatest for the frontal pair, suggesting a greater recruitment of frontal coherence for inhibitory control. For long distance intrahemispheric pairs, increased coherence for No-go trials was greater for the fronto-parietal pair for the delta and theta bands, whereas increased coherence was greater for the fronto-occipital pair for alpha, beta, and gamma. Overall, this suggests that there is a greater recruitment of coordinated brain activity in the fronto-parietal network (both cross-hemisphere and within-hemisphere) when performing the more cognitively demanding No-go trials requiring inhibitory control. This is consistent with previous studies in healthy young adults, which have found that tasks that require the inhibition of a response, or the production of a different response of an infrequent stimulus result in increased cross-hemisphere frontal coherence and intrahemispheric anterior-posterior coherence, particularly in the theta band (e.g., Brier et al., 2010; Harmony et al., 2009; Qassim et al., 2013). The results of the present study extend these findings to older adults and individuals with mild cognitive impairment and AD, showing that tasks of inhibitory control elicit increased cross-hemisphere frontal and intrahemispheric fronto-parietal coherence in these groups as well, and that this effect can be seen across frequency bands.

3.5.3 EEG Coherence: Group Differences

3.5.3.1 Alzheimer's disease. We also examined group differences in coherence during Go and No-go trials as well as group differences with respect to the change in coherence with the addition of inhibitory control demands. AD patients showed reduced cross-hemisphere frontal theta coherence for inhibition trials and reduced parietal theta coherence for both inhibition and non-inhibition trials. Furthermore, AD patients showed less of an increase in frontal theta coherence for inhibition trials. Fronto-parietal coherence was not affected in AD patients. No

previous studies have examined EEG coherence in AD during the performance of the Go/No-go task; however, two studies have examined EEG coherence during sustained attention (visual oddball task). In one study, both inter- and intra-hemisphere electrode pairs were examined, and AD patients exhibited decreased coherence only for fronto-parietal pairs in the lower frequency bands (delta and theta) (Güntekin et al., 2008). In the second study, only intrahemispheric fronto-parietal, fronto-temporal, and fronto-occipital pairs were examined, and coherence was found to be reduced in AD patients for all pairs in the delta, theta, and alpha bands (Başar et al., 2010). In contrast, in the present study, EEG coherence during Go trials, which may involve similar sustained attention processes, was reduced for the cross-hemisphere parietal pair only. Differences between the tasks used may account for the different findings, and future research is needed to clarify whether reductions in intra- versus inter-hemispheric coherence is task specific.

The results of the present study can be directly compared to a concurrent study that used the same participants to examine EEG coherence while at rest (Johns et al., 2015), and found that AD patients demonstrated reduced cross-hemisphere parietal coherence in the delta and theta bands. In the present study, Go trials (sustained attention) did not elicit any further reductions in coherence than what is observed while at rest; however, during No-go trials, AD patients exhibited an additional reduction in cross-hemisphere frontal coherence in comparison to normal controls. No-go trials elicited increased coherence in comparison to Go trials for control participants, but AD patients failed to increase frontal coherence to the same degree in response to inhibitory task demands.

3.5.3.2 Mild cognitive impairment. With regards to the group differences between MCI patients and controls, the effect of trial type differed between the two groups for the theta and alpha bands. In the theta band, though coherence values did not differ between MCI patients and controls for either Go or No-go trials, the increase in frontal coherence for No-go trials was notably smaller for MCI patients than for controls. In other words, MCI patients failed to increase frontal coherence in response to inhibitory task demands to the same extent as normal controls. In the alpha band, MCI patients demonstrated higher coherence than controls for long distance intrahemispheric pairs during No-go trials, and a greater increase in coherence for No-go trials in comparison to Go trials. Thus, the increase in coherence inhibition trials is reduced for cross-hemisphere frontal regions in the theta band and increased for fronto-parietal regions in the alpha band.

No previous studies have examined EEG coherence during the Go/No-go task or any other inhibitory control task in MCI patients; however, there have been studies that examined EEG coherence or synchronization during the performance of short-term memory (Bajo et al., 2010; Pijnenburg et al., 2004) and working memory (Jiang, 2005b; Jiang et al., 2008; L.-L. Zheng et al., 2007) tasks. The finding of a reduced change in theta coherence as a function of task demands in the present study has not been previously reported in studies of task-related coherence. Few studies have examined theta coherence during task performance, and those that have did not examine the change in coherence as a function of task (Jiang, 2005b; Jiang et al., 2008; Pijnenburg et al., 2004). This is the first study to report findings that suggest that, while MCI patients may not differ from controls in coherence measured during task performance, there may be a deficit in the amount that coherence increases in response to increasing task demands. Specifically, we found that during a task of inhibitory control, which elicited increased interhemispheric frontal theta coherence on inhibition trials in normal controls, MCI patients exhibited a smaller increase for inhibition trials. MCI patients appeared to have somewhat higher frontal theta coherence during Go trials (though the difference did not reach statistical significance), therefore it is possible that the less cognitively demanding trials require more frontal theta coherence for MCI patient than normal controls, and MCI patients are left with less "room" to increase coherence on the more cognitively demanding No-go trials.

The finding of increased fronto-parietal alpha coherence in MCI patients but not AD patients in the present study is consistent with previous reports of overall higher synchronization in the alpha band during task performance (Pijnenburg et al., 2004). However, in another study, increased alpha coherence was reported only for cross-hemisphere anterior regions (Bajo et al., 2010). Therefore, increased alpha coherence in MCI patients during task performance appears to be emerging as a consistent finding across studies using different tasks; however, the regions involved may vary depending on the task used. This increase in alpha coherence may represent a compensatory mechanism or an attempt at neural compensation, which breaks down with disease progression. Similar results have been reported in fMRI studies, which have found increased activation in early-stage MCI during executive functioning tasks, which is no longer present in late-stage MCI (e.g., Clément et al., 2013).

3.5.4 Correlational Analyses

3.5.4.1 Relationships between EEG coherence and neuropathology. As we were interested to know whether EEG coherence during the performance of a cognitive task was related to measures of brain integrity, we examined correlations between EEG coherence during the Go/No-go task (coherence difference between No-go and Go trials) and measures of cortical thickness and PiB retention. The relationship between EEG coherence and cortical thickness was variable across the three groups. There was no consistent relationship between EEG coherence and cortical thickness in normal controls. However, in MCI patients, cross-hemisphere parietal coherence was reliably negatively associated with prefrontal and parietal cortical thickness for both the delta and theta bands. The reverse pattern was seen in AD patients, where cross-hemisphere parietal coherence was positively associated with prefrontal cortical thickness for the theta and gamma bands. To focus on the theta band, which has been associated with tasks of inhibitory control (e.g., Brier et al., 2010; Harmony et al., 2009; Qassim et al., 2013), cross-hemisphere parietal coherence was positively associated with prefrontal cortical thickness in normal controls and AD patients, but negatively associated with prefrontal and parietal thickness in MCI patients. It could be hypothesized that the reverse relationship seen in MCI patients, which is indicative of increasing coherence with decreasing cortical thickness, is a compensatory process in which increased parietal coherence reflects an attempt at compensation for decreased cortical thickness, but that this process breaks down in AD. This is an interesting possibility; however, it is speculative at this point.

With regards to the relationship between EEG coherence and PiB retention, the overall pattern indicated that MCI patients once again exhibited a different relationship between these variables than normal controls and AD patients. In normal controls and AD patients, higher PiB retention was associated with lower coherence in the beta and gamma bands. In contrast, in MCI patients, higher PiB retention was associated with higher coherence in the beta band. Once again, one could speculate that the increased coherence associated with increased neuropathology is reflective of a compensatory neural process in MCI patients. It is also interesting to note that the reliable correlations were primarily with cross-hemisphere frontal gamma coherence in normal controls and with cross-hemisphere parietal beta coherence in MCI patients. As PiB retention was elevated only in frontal regions in MCI patients, one might speculate that amyloid deposition in the frontal lobes prevents compensatory increases in cross-hemisphere frontal

coherence, but that cross-hemisphere parietal coherence is increased as an attempt to compensate for neuropathology in the frontal lobes. Future studies are needed to replicate these findings in order to determine whether this is a reliable difference between the two groups.

There is also an interesting comparison that can be made for the relationship between EEG coherence and PiB retention when coherence is measured at rest versus during the performance of a cognitive task. In our concurrent study that examined resting coherence using the same participants (Johns et al., 2015), we found that higher PiB retention was associated with higher resting fronto-parietal coherence in normal controls; however, in the present study, we found no relationship between fronto-parietal coherence during the Go/No-go task and PiB retention. In addition, there was a negative association between PiB retention and cross-hemisphere frontal and parietal coherence both at rest and during the Go/No-go task. Thus, normal controls with higher PiB retention may have a higher baseline level of resting fronto-parietal coherence, which results in less "room" to increase coherence in response to task demands. In contrast, MCI patients with higher PiB retention exhibited lower resting frontal and fronto-parietal coherence, but more of an increase in parietal coherence for inhibition trials during the Go/No-go task. Thus, the opposite pattern is found in MCI patients: individuals with higher PiB retention have lower baseline coherence, but coherence is more responsive to task demands. Possibly this different pattern of results suggests that compensatory processes in response to neuropathological burden may be different in individuals with normal cognitive function in comparison to those with MCI.

3.5.4.2 Relationships between neuroimaging measures and Go/No-go performance. Patients with AD and MCI had slower reaction times on the Go/No-go task, which was associated with lower parietal alpha coherence and greater frontal cortical thickness for MCI patients and with higher PiB retention in the anterior cingulate cortex in AD patients. Lower accuracy on the Go/No-go task was associated with higher parietal alpha coherence and higher fronto-parietal theta coherence for MCI patients, and with higher parietal and fronto-parietal alpha coherence for AD patients. There were no associations between performance on the Go/No-go task and neuroimaging measures in normal controls. The lack of a relationship between EEG coherence during the Go/No-go task and performance on the task in normal controls is somewhat surprising, as one might predict that brain functioning during a task would be related to task performance. However, the relationship between functional connectivity and

cognition may be more complex than a simple linear relationship between the two variables, and may be moderated by other factors such as neurocognitive reserve, neuropathological burden, task strategies, and/or the use of potential compensatory mechanisms.

It is also interesting to note that the EEG coherence variables that were found to be affected in AD and MCI patients in the group comparison (frontal theta coherence for both AD and MCI patients and fronto-parietal alpha coherence for MCI patients) did not show a reliable relationship with other measures of neuropathology or with performance on the Go/No-go task. Once again, this could reflect that the relationship between brain integrity, functional connectivity, and cognitive performance is more complex than the simple linear relationships that we were able to explore in the present study. Furthermore, changes in brain functioning may be more closely related to other measures of neuropathology (such as white matter tract integrity) that were not assessed in this study.

3.5.5 Implications

The present study makes several important contributions to our understanding of inhibitory control abilities in AD and MCI patients. First, we confirmed the presence of deficits on tasks of inhibition in both patient groups, particularly for semantic inhibition, as measured by the Hayling test. Second, we measured EEG coherence during the performance of a task of inhibitory control, and found that EEG coherence was reliably increased by inhibitory control demands in the three groups, and particularly for frontal and fronto-parietal electrode pairs. Third, we found that there are group differences in how EEG coherence is modulated by inhibitory task demands within a fronto-parietal network. Both AD patients and MCI patients exhibited reduced modulation of cross-hemisphere frontal theta connectivity during the Go/No-go task that was not found for resting coherence, and MCI patients additionally showed increased intrahemispheric alpha coherence during inhibition trials that was not found for resting coherence. Thus, AD and MCI patients exhibit altered functional connectivity that may only be detectable when performing a cognitive task, and specifically a task that taps into executive fronto-parietal functions. A fourth implication of these results is that additional information about functional connectivity in MCI and AD may be gained by examining changes in coherence in response to task demands. Specifically, although cross-hemisphere frontal theta coherence did not differ between MCI patients and normal controls during either Go or No-go trials, the degree to which coherence was modulated for No-go trials versus Go trials was smaller for MCI patients.

In fact, the increase in coherence elicited by inhibition trials was similar to that of AD patients, despite an overall higher level of coherence in MCI patients. Thus, coherence changes in response to task demands may provide additional important information about changes in functional connectivity in the early stages of dementia.

Finally, there is some evidence of a potential compensatory increase in functional connectivity within a fronto-parietal network during the performance of a task of inhibitory control in MCI patients. First, MCI patients showed higher intrahemispheric alpha coherence during No-go trials and a greater increase in intrahemispheric alpha coherence with inhibitory task demands in comparison to normal controls. Second, MCI patients demonstrated a reverse pattern in the relationship between EEG coherence during task performance and measures of neuropathology (cortical thickness and PiB retention) in comparison to normal controls and AD patients. Specifically, in MCI patients, reduced cortical thickness in was associated with increased cross-hemisphere frontal and parietal coherence in the lower frequency bands, whereas higher PiB retention was associated with higher cross-hemisphere parietal coherence in the beta band. Thus, increased EEG coherence may reflect functional compensation for increased neuropathology in MCI patients, but this compensatory process may break down as the disease progresses. Future studies with larger sample sizes would enable the use of more sophisticated statistical analysis techniques to further elucidate the interrelationships between these variables.

3.5.6 Strengths and Limitations

This is the first study to examine EEG coherence during the performance of a task of inhibitory control in patients with AD and MCI. A major strength of the study is the use of a well-established task of inhibitory control, a cognitive domain that is known to be affected in MCI and AD. This is also the first study to directly examine the relationships between EEG coherence during a cognitive task and cortical thickness and PiB retention in AD and MCI patients. However, we were limited in our ability to draw strong conclusions from the correlational analysis and to use more sophisticated statistical techniques due to the small sample size for the correlational analysis, particularly for cortical thickness and PiB retention for AD patients and controls.

It should also be noted that, due to practical constraints, there was a time delay between the EEG testing and the measurement of cortical thickness and PiB retention. Thus, it is possible that neuropathological changes occurred between the testing sessions, which may have affected

the correlations between these variables. Obtaining neuropathological measures closer in time to measures of EEG coherence would be beneficial in future studies. Finally, as with any EEG study, we are limited in our ability to draw specific conclusions about the neural sources generating the changes in EEG coherence, due to the relatively poor spatial resolution of EEG. We have assumed that activity recorded at frontal sites reflects primarily frontal cortical activity, and activity recorded at parietal sites reflects primarily parietal cortical activity; however, we cannot be more specific than that regarding the localization of the signal generated.

3.5.7 Conclusions and Future Directions

Overall, the results from the present study point to altered functional connectivity within a fronto-parietal network during the performance of a task of inhibitory control in both AD and MCI patients. Both AD and MCI patients exhibited deficits in frontal connectivity in the theta band, and MCI patients exhibited increased fronto-parietal connectivity in the alpha band. It is difficult to interpret the relationship between EEG coherence, neuropathology, and cognition in cross-sectional studies due to inter-individual variability on factors such as the stage of the illness, level of cognitive functioning, neurocognitive reserve, the use of compensatory mechanisms, and whether neural compensation mechanisms are successful or unsuccessful. These factors can be addressed in longitudinal studies that examine changes within subjects over the course of progression from normal cognitive function to dementia. Furthermore, longitudinal studies may also address the effects of various treatments (e.g., acetylcholinesterase inhibitors) on EEG coherence and cognition, and the effects of cognitive training in executive functioning tasks on EEG coherence in order to elucidate the relationship between these factors.

Table 3.1.

Summary Data for Demographics, Clinical Screening Tests, Neuropsychological Test Scores, Cortical Thickness, and PiB Retention

	NEC			MCI			AD			Group
Variable	***n***	***M***	***SD***	***n***	***M***	***SD***	***n***	***M***	***SD***	**Differences[a]**
Demographics										
Age	26	78.2	4.4	21	80.2	5.7	16	79.7	5.5	n.s.
Education	26	14.4	4.0	21	13.7	4.1	16	13.8	2.9	n.s.
Sex (% Female)	26	57.7	--	21	52.4	--	16	25.0	--	n.s.
Screening Tests										
GDS	26	1.4	1.7	21	1.6	1.7	16	2.0	1.7	n.s.
SMCS	26	3.1	2.7	21	4.7	2.4	16	6.8	5.4	AD>NEC
MoCA	26	27.6	1.5	21	22.5	4.3	16	19.3	4.3	AD<MCI<NEC
Neuropsychological Tests										
Similarities (Total /33)	26	24.5	4.4	21	19.1	4.3	16	17.4	6.6	AD=MCI<NEC
Symbol Search (Total /60)	26	25.4	5.4	19	19.5	7.3	16	13.9	9.2	AD<MCI<NEC
Digit Span Forward (Total /16)	26	6.6	1.2	11	5.6	1.6	14	5.1	0.9	AD<NEC[b]
Digit Span Backwards (Total /14)	26	5.1	1.4	11	4.1	1.3	14	4.1	0.9	n.s.[c]
Boston Naming Test (Total /15)	26	13.7	1.5	21	12.3	3.7	16	8.9	3.5	AD<MCI=NEC
CVLT Total Learning Trials (max /80)	26	46.0	7.0	21	30.8	8.2	16	22.2	7.2	AD<MCI<NEC
CVLT Long Delay (max /16)	26	10.3	3.2	21	3.9	3.6	16	1.3	1.9	AD<MCI<NEC
Letter Number Sequencing (Total /21)	26	9.9	3.0	12	8.1	1.7	12	6.6	3.2	AD<NEC[b]
Phonemic Fluency (Total Words: FAS)	25	42.5	10.9	20	36.2	11.8	16	29.8	12.5	AD<NEC
Semantic Fluency (Total Words: Animals)	25	17.8	4.1	20	12.7	4.3	16	9.1	4.3	AD<MCI<NEC
Trail Making Test Time in sec. (B/A)	22	2.8	1.5	14	2.8	1.1	14	4.0	2.9	n.s.[c]
Stroop Victoria Time in sec. (Colour/Dots)	26	1.8	0.5	13	2.2	0.7	14	2.1	0.5	n.s.
Stroop Victoria Errors (Colour – Dots)	26	0.1	0.4	13	1.7	2.1	14	2.6	4.3	AD>NEC
Hayling Test Time in sec. (Condition 2/1)	25	8.3	6.7	18	8.9	6.3	14	4.6	8.8	n.s.
Hayling Test Errors Scaled Score[d]	25	7.0	1.6	18	4.9	2.6	14	4.1	2.7	AD=MCI<NEC
Hayling Test Total Scaled Score	25	5.8	1.4	18	4.4	1.9	14	2.2	1.6	AD<MCI<NEC
Cortical Thickness										
Superior frontal gyrus	7	3.04	0.2	17	2.92	0.2	7	2.82	0.2	n.s.
Middle frontal gyrus	7	2.99	0.2	17	2.85	0.2	7	2.85	0.2	n.s.
Anterior cingulate cortex	7	3.63	0.2	17	3.45	0.2	7	3.39	0.2	AD<NEC[b]

Superior parietal lobule	7	2.67	0.3	17	2.57	0.2	7	2.60	0.2	n.s.
Parahippocampal gyrus	7	3.45	0.1	17	3.25	0.2	7	2.93	0.1	AD<MCI<NEC
PiB Retention										
Superior frontal gyrus	10	1.06	0.1	13	1.35	0.4	7	1.42	0.3	AD, MCI>NEC
Middle frontal gyrus	10	1.13	0.2	13	1.40	0.4	7	1.52	0.3	AD>NEC[b]
Anterior cingulate cortex	10	1.44	0.2	13	1.79	0.6	7	1.90	0.4	AD>NEC[b]
Superior parietal lobule	10	1.15	0.2	13	1.33	0.5	7	1.54	0.3	AD>NEC
Hippocampus	10	1.39	0.1	13	1.46	0.2	7	1.31	0.1	AD<MCI
Parahippocampal gyrus	10	1.19	0.1	13	1.26	0.2	7	1.21	0.1	n.s.

Note. Due to a change in the procedure for the administration of the neuropsychological test battery at the memory clinic during the period of data collection for this study, certain neuropsychological tests are missing data for some participants, as indicated in the table above. NEC = normal elderly controls; MCI = mild cognitive impairment; AD = Alzheimer's disease; GDS = Geriatric Depression Scale; SMCS = Subjective Memory Complaints Scale; MoCA = Montreal Cognitive Assessment; CVLT = California Verbal Learning Test. [a]Group differences noted in this column are at a significance level of $p < .05$. [b]$p < .10$ for MCI<NEC. [c]$p < .10$ for AD<NEC. [d]Higher scores indicate better performance.

Table 3.2.
ANOVA Results: EEG Coherence During the Go/No-go Task for Cross-hemisphere Homologous Pairs

	F	df	*p*	η^2_p	ε	sig.	Post-hoc[a]
Delta							
Trial Type	23.72	1, 60	<.001	.28	--	**	Go<No-go
Electrode Pair x Trial Type	5.74	2, 120	.020	.09	.963	*	Go<No-go (F3-F4, P3-P4)
Theta							
Trial Type	63.15	1, 60	<.001	.51	--	**	Go<No-go
Group	4.73	2, 60	.012	.14	--	*	AD<MCI=NEC
Electrode Pair x Trial Type	9.75	2, 120	<.001	.14	.862	**	Go<No-go (all pairs)
Electrode Pair x Trial Type x Group	2.84	4, 120	.035	.09	.862	*	See text
Alpha							
Trial Type	43.49	1, 60	<.001	.42	--	**	Go<No-go
Beta							
Trial Type	84.07	1, 60	<.001	.58	--	**	Go<No-go
Electrode Pair x Trial Type	20.26	2, 120	<.001	.25	.927	**	Go<No-go (all pairs)
Gamma							
Condition	33.55	1, 60	<.001	.36	--	**	Go<No-go
Electrode Pair x Trial Type	49.51	2, 120	<.001	.45	.969	**	Go<No-go (F3-F4, P3-P4)

Note. [a]$p < .05$. ** $p < .01$. * $p < .05$.

Table 3.3.
ANOVA Results: EEG Coherence During the Go/No-go Task for Long Distance Intrahemispheric Pairs

	F	df	*p*	η^2_p	sig.	Post-hoc
Delta						
Trial Type	52.66	1, 60	<.001	.47	**	Go<No-go
Electrode Pair x Trial Type	20.86	1, 60	<.001	.26	**	Go<No-go (both pairs) Difference between trial types: F3-P3>F3-O1
Theta						
Trial Type	115.28	1, 60	<.001	.66	**	Go<No-go
Electrode Pair x Trial Type	7.46	1, 60	.008	.11	**	Go<No-go (both pairs) Difference between trial types: F3-P3>F3-O1
Alpha						
Trial Type	94.38	1, 60	<.001	.61	**	Go<No-go
Electrode Pair x Trial Type	6.38	1, 60	.014	.10	*	Go<No-go (both pairs) Difference between trial types: F3-P3<F3-O1
Trial Type x Group	2.84	2, 60	.066	.09	+	No-go: MCI>NEC (trend for MCI>AD) Difference between trial types: MCI>AD (trend for MCI>NEC)
Beta						
Trial Type	180.36	1, 60	<.001	.75	**	Go<No-go
Electrode Pair x Trial Type	4.11	1, 60	.047	.06	*	Go<No-go (both pairs) Difference between trial types: F3-P3<F3-O1
Trial Type x Group	2.68	2, 60	.077	.08	+	Difference between trial types: AD>MCI
Gamma						
Trial Type	58.55	1, 60	<.001	.49	**	Go<No-go
Electrode Pair x Trial Type	3.88	1, 60	.053	.06	+	Go<No-go (both pairs) Difference between trial types: F3-P3<F3-O1

Note. [a]$p < .05$. ** $p < .01$. * $p < .05$. + $p < .01$.

Table 3.4.

Correlations Between Neuroimaging Measures and Between Neuroimaging and Go/No-go Performance

	Normal Elderly Controls			Mild Cognitive Impairment			Alzhiemer's Disease		
Neuroimaging Measures	**Variables**	***r***	***p***	**Variables**	***r***	***p***	**Variables**	***r***	***p***
Go/no-go Coherence & Cortical Thickness				Delta F3-F4 & Superior Frontal Gyrus	-.566	.018			
	Delta P3-P4 & Anterior Cingulate Cortex	-.765	.045	**Delta P3-P4 & Middle Frontal Gyrus**	**-.822**	**<.001**	Theta P3-P4 & Middle Frontal Gyrus	.839	.018
	Theta P3-P4 & Middle Frontal Gyrus	.766	.045	Theta P3-P4 & Superior Frontal Gyrus	-.491	.045	Gamma P3-P4 & Anterior Cingulate Cortex	.828	.021
				Theta P3-P4 & Superior Parietal Lobule	-.572	.016			
Go/no-go Coherence & PiB Uptake	**Gamma F3-F4 & Superior Frontal Gyrus**	**-.814**	**.004**				Beta F3-F4 & Superior Parietal Lobule	-.815	.026
	Gamma F3-F4 & Middle Frontal Gyrus	**-.864**	**.001**						
	Gamma F3-F4 & Anterior Cingulage Cortex	**-.793**	**.006**						
	Beta P3-P4 & Superior Parietal Lobule	-.663	.037	**Beta P3-P4 & Superior Frontal Gyrus**	**.689**	**.009**			
	Gamma P3-P4 & Anterior Cingulate Cortex	-.718	.019	Beta P3-P4 & Middle Frontal Gyrus	.674	.012			
				Beta P3-P4 & Anterior Cingulate Cortex	**.697**	**.008**			
				Beta P3-P4 & Superior Parietal Lobule	**.777**	**.002**			
							Beta F3-P3 & Superior Parietal Lobule	-.789	.035

Neuroimaging & Go/No-go Behaviour	**Variables**	***r***	***p***	**Variables**	***r***	***p***	**Variables**	***r***	***p***
Go/no-go Coherence & Go/no-go Behaviour	None			**Alpha P3-P4 & Go/no-go Accuracy**	**-.600**	**.004**	**Alpha P3-P4 & Go/no-go Accuracy**	**-.670**	**.006**
				Alpha P3-P4 & Go/no-go RT	-.522	.015			
				Theta F3-P3 & Go/no-go Accuracy	-.476	.029	Alpha F3-P3 & Go/no-go Accuracy	-.532	.041
Cortical Thickness & Go/no-go Behaviour	None			Middle Frontal Gyrus & Go/no-go RT	.585	.014	None		
PiB Uptake & Go/no-go Behaviour	None			None			Anterior Cingulate Cortex & Go/no-go RT	.763	.046

Note. In each cell, significant correlations are grouped by electrode pair (F3-F4 is presented first, followed by P3-P4, then F3-P3). Bolded entries indicate $p < .01$.

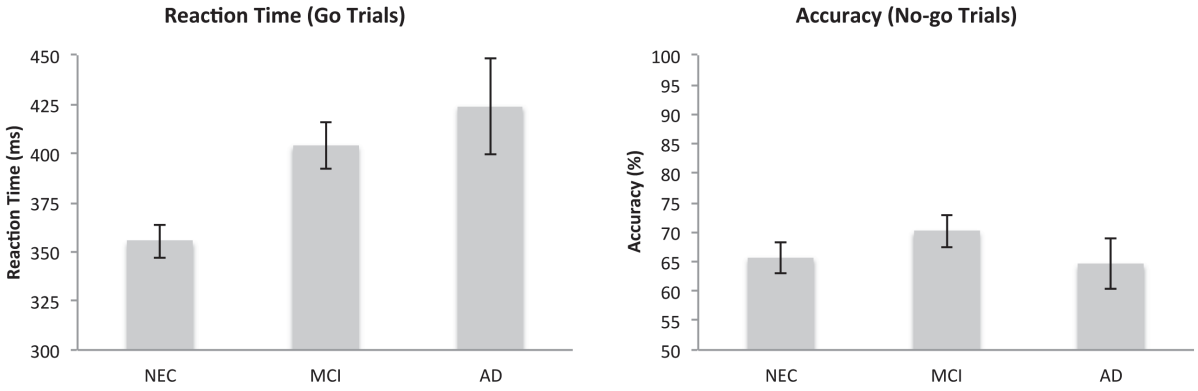

Figure 3.1. Reaction time for Go trials and accuracy for No-go trials for the Go/No-go task for patients with Alzheimer's disease (AD), patients with mild cognitive impairment (MCI), and normal elderly controls (NECs). Error bars represent one standard error of the mean.

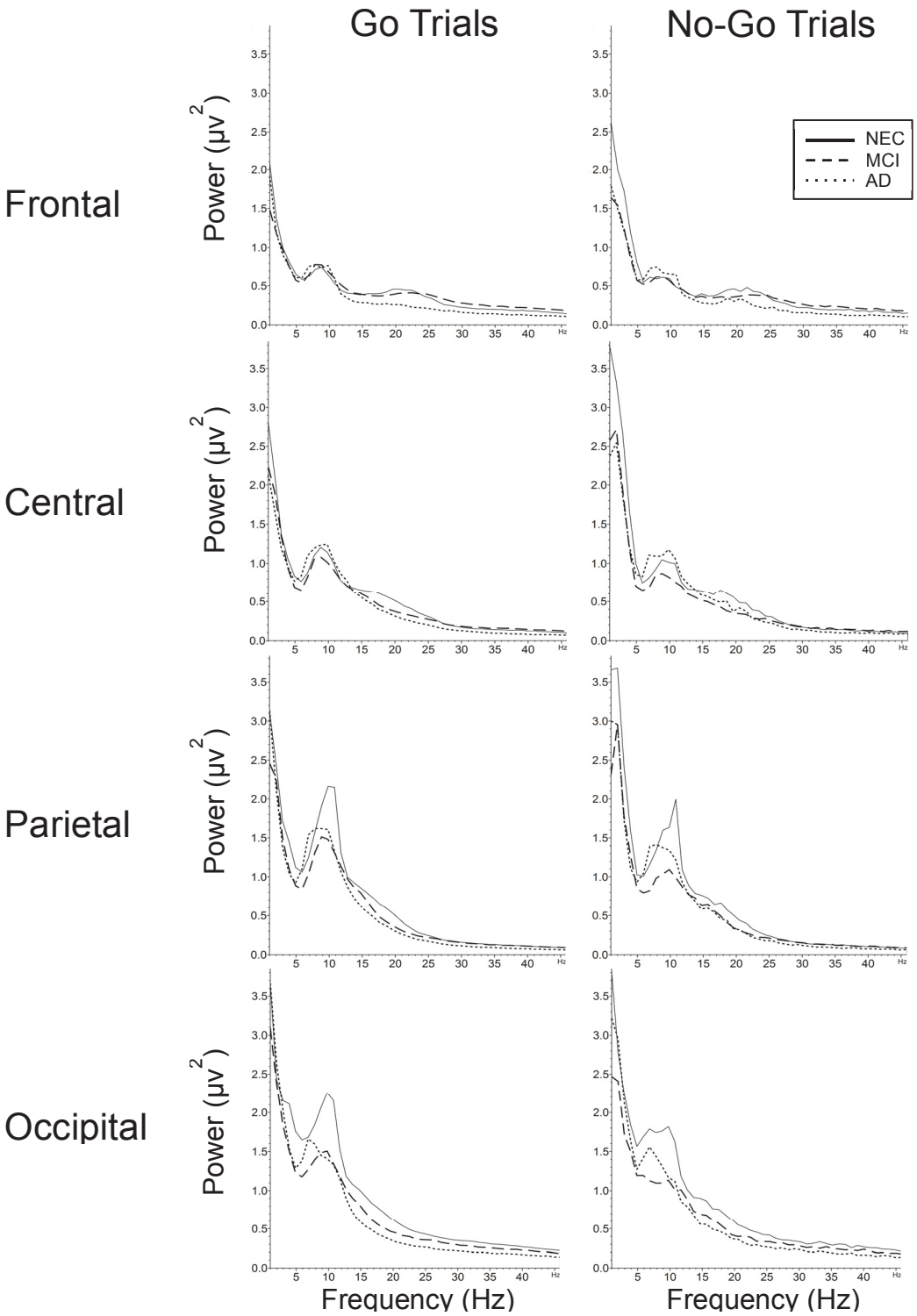

Figure 3.2. Mean power during Go and No-go trials at frontal (F3, Fz, F4), central (C3, Cz, C4), parietal (P3, Pz, P4), and occipital (O1, O2) electrode sites for normal elderly controls (NEC), patients with mild cognitive impairment (MCI), and patients with Alzheimer's disease (AD).

Theta Coherence During the Go/No-go Task

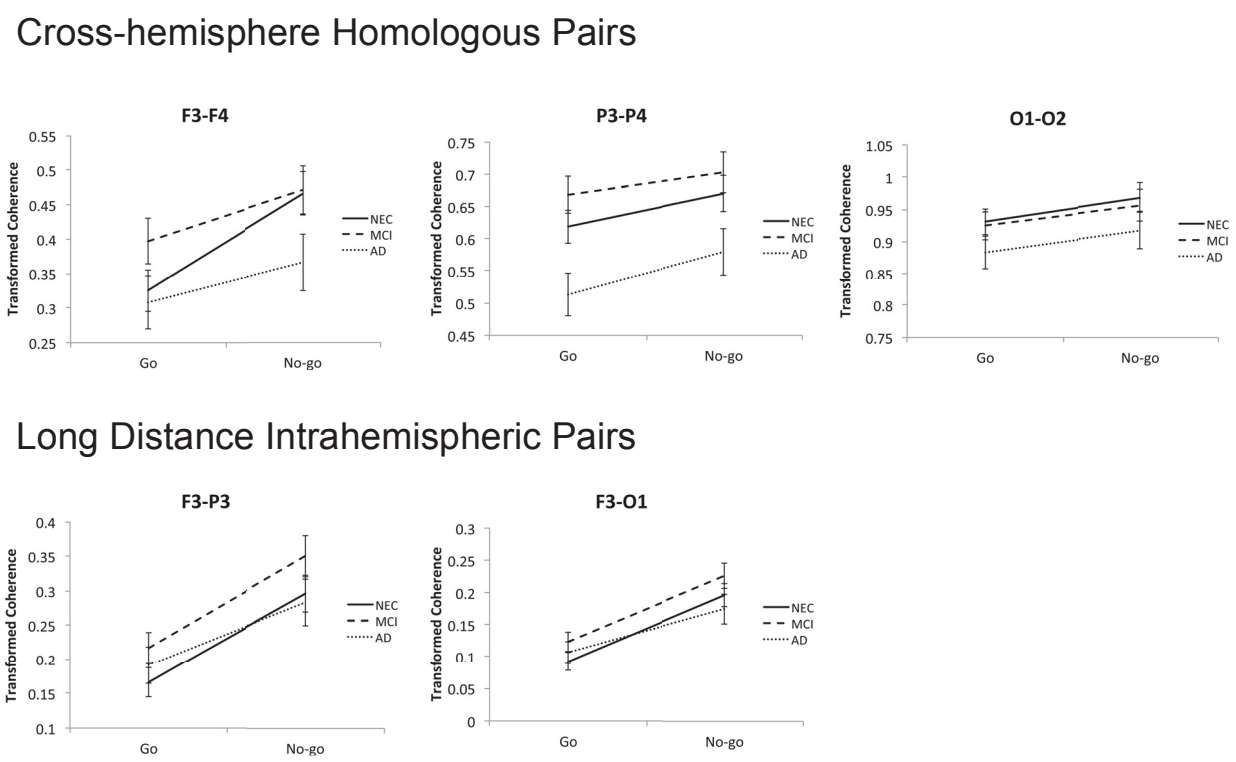

Figure 3.3. Theta EEG coherence values for Normal Elderly Controls (NECs), patients with mild cognitive impairment (MCI), and patients with Alzheimer's disease (AD) during the Go/No-go task. Data are square root and Fisher's Z transformed. Error bars represent the standard error of the mean. Note that the scale on the y-axis varies by electrode pair, though the range remains constant.

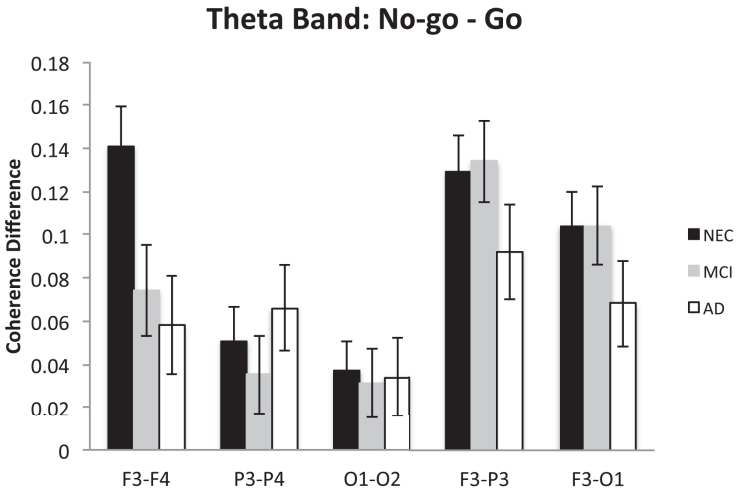

Figure 3.4. Theta band EEG coherence difference scores for No-go trials minus Go trials for Normal Elderly Controls (NECs), patients with mild cognitive impairment (MCI), and patients with Alzheimer's disease (AD). Data are square root and Fisher's Z transformed. Error bars represent the standard error of the mean.

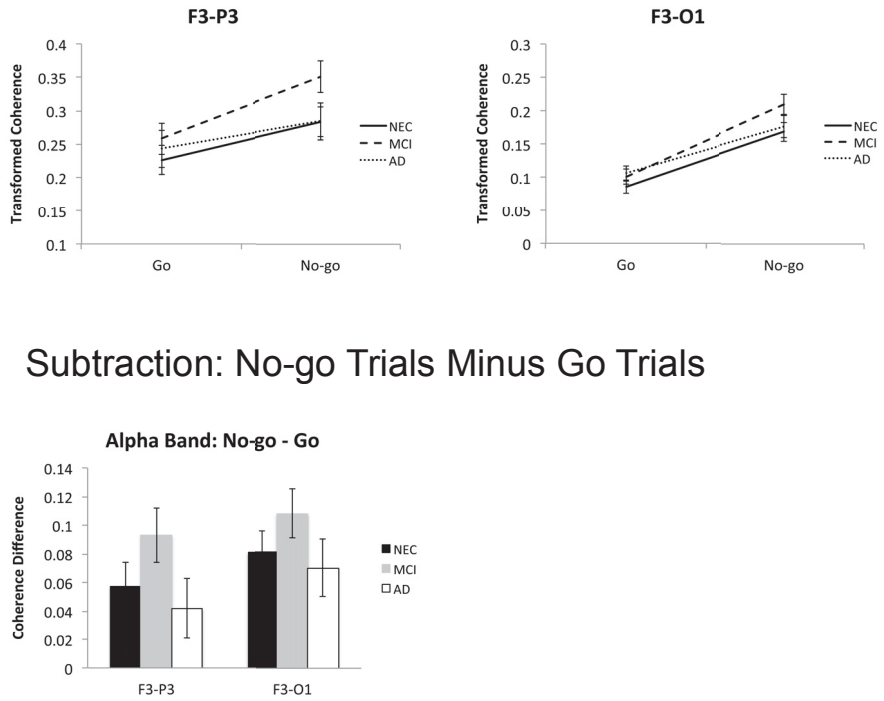

Figure 3.5. Alpha band EEG coherence difference scores for long distance intrahemispheric pairs for Normal Elderly Controls (NECs), patients with mild cognitive impairment (MCI), and patients with Alzheimer's disease (AD). Data are square root and Fisher's Z transformed. Error bars represent the standard error of the mean.

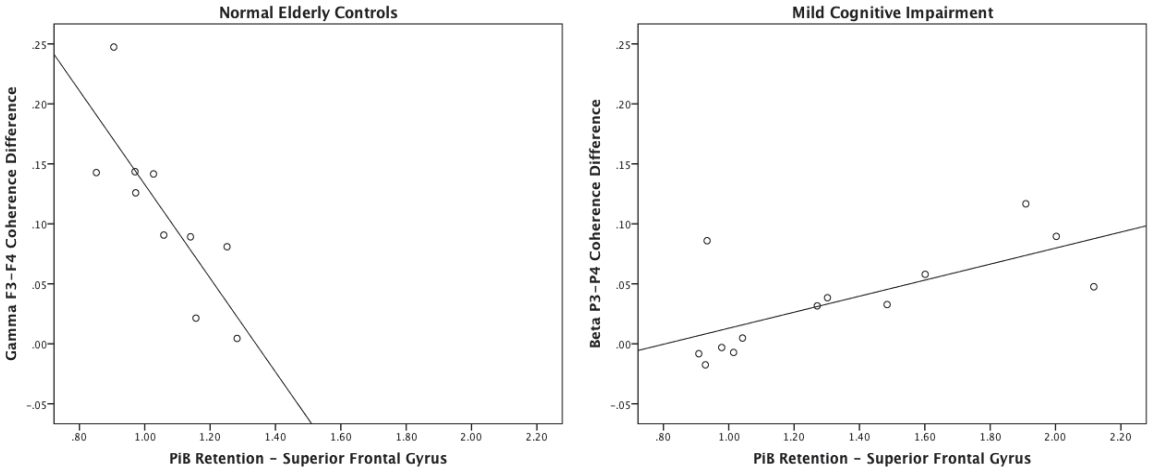

Figure 3.6. Sample scatterplots for EEG coherence difference (No-go trials minus Go trials) and PiB retention in normal elderly controls (gamma F3-F4) and mild cognitive impairment (beta P3-P4).

CHAPTER 4: STUDY 3

EEG Coherence and Working Memory in
Mild Cognitive Impairment and Alzheimer's Disease

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4.1 Abstract

Objective: Our primary aim was to examine the relationship between EEG coherence and working memory (WM) in patients with mild cognitive impairment (MCI), Alzheimer's disease (AD), and normal elderly controls (NECs). *Methods:* We recorded EEG during an N-back (0- to 2-back) WM task for 21 MCI patients, 16 AD patients, and 26 NECs. EEG coherence was calculated for a selection of electrode pairs within a fronto-parietal network for the delta, theta, alpha, beta, and gamma bands, and we explored correlations between coherence, behavioural performance, and measures of brain integrity (cortical thickness and PiB retention). *Results:* Behavioural results showed that AD patients had longer reaction times for the 1-back condition, and lower accuracy for all WM loads, while MCI patients had lower accuracy for the 2-back condition. EEG coherence was differentially modulated by WM load depending on group, electrode pair, and frequency band. Compared to NECs, AD patients showed reduced cross-hemisphere (delta, theta, alpha) and fronto-parietal (delta) coherence, and a smaller increase in cross-hemisphere beta and fronto-parietal theta coherence with WM load. MCI patients also exhibited alterations in WM-related modulation of coherence (smaller decrease for frontal alpha, smaller increase for frontal beta, greater increase for fronto-parietal beta). Correlations with measures of brain integrity were suggestive of a possible compensatory increase in coherence in NECs and MCI patients with increasing pathological burden. *Conclusion:* AD patients demonstrate reduced functional connectivity within a fronto-parietal network during a working memory task, and both AD and MCI patients show alterations in WM-related modulation of EEG coherence, with possible compensatory increases in coherence at lower WM loads in MCI patients.

Keywords: Alzheimer's disease (AD), mild cognitive impairment (MCI), electroencephalography (EEG), EEG coherence, working memory, N-back, executive functioning, PiB, cortical thickness

4.2 Introduction

Although Alzheimer's disease is typically thought of as primarily involving deficits in episodic memory, difficulties with executive functioning are increasingly being recognized as an important aspect of early Alzheimer's disease (AD) and mild cognitive impairment (MCI) (Johns et al., 2012; Perry & Hodges, 1999; Weintraub et al., 2012). The neurological underpinnings of executive dysfunction in MCI and AD remain unclear; however, it has been posited that alterations to functional neuronal networks may play a role (e.g., Bokde et al., 2009; Delbeuck et al., 2003; D. P. Salmon & Bondi, 2009).

Executive functioning can be defined as higher level cognitive control over lower level cognitive functions (Diamond, 2013), and it is made up of several components, including working memory, response inhibition, divided attention, planning, judgment, decision-making, and cognitive flexibility (Diamond, 2013; Goldstein et al., 2014; Stuss & Alexander, 2000; Stuss & Levine, 2002). Though executive functions have long been linked the frontal lobes, it is now generally agreed that a network of both frontal and non-frontal regions supports intact executive functioning (for reviews, see Collette et al., 2006; Gazzaley & D'Esposito, 2007; Stuss & Levine, 2002). This makes intuitive sense, given that the lower level cognitive functions coordinated by executive functioning are supported by non-frontal brain regions. Numerous functional neuroimaging studies have also found that executive functioning tasks activate the prefrontal cortex as well as posterior regions (mainly in the parietal cortex) (for reviews, see Chung et al., 2014; Collette et al., 2006).

The focus of the present study is on working memory, an important aspect of executive functioning, defined as the ability to manipulate information that is held in mind (Baddeley, 1992; Diamond, 2013). The N-back task is commonly used to investigate the neurological underpinnings of working memory. Studies using the n-back task consistently report activations of multiple brain regions, including the dorsolateral prefrontal cortex, ventrolateral prefrontal cortex, supplementary motor area, premotor cortex, and posterior parietal areas (for reviews, see Baddeley, 2003; Chung et al., 2014; Collette et al., 2006; D'Esposito et al., 1998; Elliott, 2003; for a meta-analysis, see Owen et al., 2005). In addition, fronto-parietal connectivity, examined with functional magnetic resonance imaging (fMRI), has been found to increase as a function of working memory load in n-back tasks (Honey et al., 2002; Narayanan et al., 2005; Newton et al., 2011).

Working memory deficits have been reported in AD and MCI in multiple studies and on multiple tasks (Belleville et al., 2003; 2007; Chang et al., 2010; Collette, 1999; Crowell et al., 2002; Huntley & Howard, 2010; Johns et al., 2012; Kessels et al., 2011; Muangpaisan et al., 2010; Sebastian et al., 2006), including the n-back task (Borkowska et al., 2009; Guild et al., 2014; Lim et al., 2008; Rombouts et al., 2005; Waltz et al., 2004; D. Zheng et al., 2012). MCI is defined by the presence of an objective cognitive deficit but preserved functional abilities (Albert et al., 2011), and in many cases, MCI represents a prodromal phase of AD or other forms of dementia (Petersen et al., 2014). MCI patients can be classified based on the presence of an episodic memory deficit as either amnestic (aMCI) or non-amnestic (naMCI), with deficits in either a single cognitive domain or multiple domains. The most common presentation in MCI patients who later develop AD is an episodic memory impairment, though other cognitive domains may also be impaired (Albert et al., 2011).

In the later stages of AD, the neuropathology is widespread and encompasses most brain areas; however, atrophy of the frontal lobes is not typically seen in early and preclinical AD (Whitwell, Przybelski, et al., 2007b). Amyloid deposition can be detected in the frontal lobes in the early stages of AD (Berti et al., 2010; Masdeu et al., 2012), though amyloid pathology has not shown a consistent relationship with cognition (Wahlster et al., 2013). In addition, altered functional connectivity within the frontal lobes and between frontal and posterior brain areas has also been reported in AD and MCI patients. For example, resting state fMRI studies have found increased connectivity within frontal networks in AD patients (Agosta et al., 2012; Balachandar et al., 2014; K. Wang et al., 2007; L. Wang et al., 2006; H.-Y. Zhang et al., 2009; J. Zhou et al., 2010), but decreased fronto-parietal connectivity (Agosta et al., 2012; Dhanjal & Wise, 2014; K. Wang et al., 2007; Z. Wang et al., 2013). Few studies have examined resting state fMRI connectivity in MCI patients for the frontal and fronto-parietal networks; however, one study reported no difference between MCI patients and controls in fronto-parietal connectivity (Agosta et al., 2012), and increased frontal connectivity, similar to what has been observed in AD has been reported in some studies (Bai et al., 2009; Liang et al., 2011; Z. Qi et al., 2010; however, see Agosta et al., 2012 & Sorg et al., 2007).

Another way to examine functional brain connectivity is with electroencephalogram (EEG) or magnetoencephalogram (MEG) coherence or synchronization measures, which have the advantage of having a much higher temporal resolution than fMRI measures (though EEG

has a lower spatial resolution). With EEG, the electrical brain activity recorded at the scalp can be spectrally decomposed in order to examine the relative power (magnitude) of the signal at each frequency band (delta, 0.5-3.5 Hz, theta, 3.5-7.5 Hz, alpha, 7.5-12.5 Hz, beta, 7.5-30 Hz, and low gamma, 30-60 Hz), and EEG coherence can be calculated for each frequency band. EEG coherence is a reflection of functional interaction between brain regions and is a measure of the consistency of the relationship between the brain activity recorded at two electrode sites (Nunez et al., 1997). Both magnitude and phase angle contribute to coherence; however, it is most strongly influenced by phase (Nunez & Srinivasan, 2006; Srinivasan et al., 2007). Synchronization between brain regions can also be examined with other measurements for EEG and MEG data, including synchronization likelihood (a measure of both linear and non-linear relationships between the two channels), and phase coherence or synchronization.

4.2.1 Spontaneous EEG Coherence in AD and MCI

EEG coherence in AD and MCI has been most commonly examined while at rest, and the most consistent finding reported in studies of AD patients is a widespread reduction in alpha and beta coherence (C. Babiloni et al., 2011; 2015). Results in other frequency bands have been more variable, with some studies reporting no differences between AD patients and controls in the lower frequency bands (e.g., Fonseca et al., 2013; Jelles et al., 2008; Ma et al., 2014; Stam et al., 2005), and other studies reporting decreased coherence (e.g., Adler et al., 2003; C. Babiloni, Ferri, et al., 2006b; Knott et al., 2000; Sankari et al., 2012). Variable results have been reported for the gamma band as well (e.g., C. Babiloni, Ferri, et al., 2004b; 2006b; Jelles et al., 2008; Koenig et al., 2005; Ma et al., 2014; Stam et al., 2005; Tao & Tian, 2005). In MCI patients, a different pattern has been reported, namely decreased resting coherence between frontal and posterior regions in all frequency bands (C. Babiloni, Ferri, et al., 2006b; Moretti et al., 2008; Tóth et al., 2014; Xu et al., 2014; however, see Tao & Tian, 2005), but no decrease in interhemispheric frontal, temporal, and parietal electrode pairs (C. Babiloni, Ferri, et al., 2006b; Jiang et al., 2008; Moretti et al., 2008; Tao & Tian, 2005; Teipel et al., 2009). Thus, alterations in the connections between frontal and posterior regions may be one of the earliest changes in functional connectivity seen in AD.

4.2.2 Event-related EEG Coherence in AD and MCI

The examination of EEG coherence during the performance of a cognitive task could be useful in providing insight into changes in brain functioning as a result of task demands. However, there are few studies that have examined EEG coherence in MCI and AD during cognitive performance. In studies that have compared EEG coherence during the performance of a cognitive task in comparison to a resting or control condition, coherence is generally higher during task performance (Başar et al., 2010). In addition, it has been reported that decreased coherence in AD patients in comparison to controls is more widespread during cognitive performance (i.e., more electrode pairs and frequency bands; Başar et al., 2010; Tao & Tian, 2005). Studies that have examined EEG coherence or synchronization in AD during the performance of a cognitive task have used measures of sustained attention (visual oddball) and short-term memory. Fronto-posterior coherence was reported to be decreased during sustained attention in the lower frequency bands (delta, theta, alpha) (Başar et al., 2010; Güntekin et al., 2008). During the performance of short-term memory tasks, decreased average synchronization likelihood has been reported in the alpha and beta bands (Pijnenburg et al., 2004), and decreased centro-temporal coherence has been reported in the alpha band (Hogan et al., 2003). Furthermore, better performance on a short-term memory task was associated with lower delta synchronization and higher alpha synchronization during the performance of the task (Pijnenburg et al., 2004). To our knowledge, no studies to date have examined EEG coherence during the performance of an executive functioning task in AD patients.

Turning now to MCI patients, previous studies have examined event-related coherence or synchronization during target counting (Tao & Tian, 2005), short-term memory tasks (Bajo et al., 2010; Pijnenburg et al., 2004), and in one set of studies, a working memory (mental addition) task (Jiang, 2005b; Jiang et al., 2008; L.-L. Zheng et al., 2007). Only the gamma band was examined in the study of target detection, and this study found reduced fronto-temporal and fronto-central coherence in comparison to controls during the performance of the task (fronto-parietal coherence was not examined) (Tao & Tian, 2005). Short-term memory was examined in two studies using synchronization likelihood, and these studies reported an overall increase in synchronization in the alpha band (Pijnenburg et al., 2004), and increased synchronization was also observed in the alpha and beta bands for interhemispheric anterior regions and for anterior and posterior regions in the gamma band (Bajo et al., 2010). In contrast, synchronization was

decreased in the alpha and beta bands for intrahemispheric temporal and central regions and for intrahemispheric temporal, central, central-posterior, and fronto-posterior regions in the gamma band (Bajo et al., 2010).

EEG coherence in MCI patients during the performance of a working memory task was examined in a set of studies using a mental addition task with three levels (Jiang, 2005b; Jiang et al., 2008; L.-L. Zheng et al., 2007). In these studies, participants were required to add two numbers either once (WM1), twice (WM2), or three times (WM3), and each of these conditions were compared to the resting condition. The effect of working memory load was examined for MCI patients and controls together in one group, and coherence was lower in the WM1 condition in comparison to the resting condition, and higher in the WM3 condition in comparison to rest for all frequency bands (delta, theta, alpha, beta) and electrode pairs (interhemispheric and intrahemispheric). With respect to group differences, while there were no differences between MCI patients and controls during the resting condition, MCI patients exhibited widespread increased coherence in comparison to controls for both inter- and intra-hemispheric electrode pairs across all frequency bands during the working memory task. This suggests that changes in functional connectivity in MCI patients may be more easily detectible during the performance of a cognitive task than while at rest.

Thus, the existing research suggests that a widespread increase in coherence involving both cross-hemisphere and long distance intrahemispheric electrode pairs and several frequency bands may be present in MCI patients (though decreased fronto-posterior gamma coherence has also been reported during task performance). This increase in event-related coherence is hypothesized to represent a compensatory mechanism needed to cope with the demands of task performance (Bajo et al., 2010; Jiang et al., 2008).

4.2.3 The Present Study

The primary goal of the present study was to examine the relationship between EEG coherence and working memory in MCI, AD, and normal elderly controls. We therefore measured EEG coherence during the performance of an N-back task of working memory. We examined electrode pairs within a fronto-parietal network, as previous research has found these areas to be activated during the performance of working memory tasks (for reviews, see Baddeley, 2003; Chung et al., 2014; Collette et al., 2006; D'Esposito et al., 1998; Elliott, 2003; for a meta-analysis, see Owen et al., 2005), and increased fronto-parietal EEG coherence has

been implicated in tasks of working memory (Mizuhara et al., 2005; Mizuhara & Yamaguchi, 2007; Sauseng et al., 2005). In this study, we examined the same participants as in two concurrent studies (Johns et al., 2015; Johns & Phillips, 2015a) in order to allow for direct comparison across studies. This enabled us to examine the relationship between EEG coherence during the performance of the N-back task and measures of neuropathology (cortical thickness and PiB retention) presented in Johns et al. (2015) as well as to directly compare the results of the present study to another study in which we examined EEG coherence during the performance of a task of inhibitory control (Johns & Phillips, 2015a).

We first examined group differences for N-back task performance and EEG coherence and then conducted several exploratory correlations in order to investigate the relationships between EEG coherence during task performance and neuropathology (cortical thickness and PiB retention) as well as cognitive performance on the N-back task. Based on the previous literature, we predicted decreased accuracy and increased reaction time for all working memory loads for AD patients, and decreased accuracy at higher working memory loads in MCI patients, as well as increased reaction time across loads. With regards to EEG coherence, based on previous studies of event-related coherence in AD and MCI, we predicted that AD patients would exhibit decreased fronto-parietal coherence in the lower frequency bands, and that this effect would be larger with increasing WM load. For MCI patients, we predicted increased coherence for both interhemispheric (frontal and parietal) and intrahemispheric (fronto-parietal) pairs, once again increasing with working memory load. With respect to the inter-correlations, due to the limited amount of previous literature in this area, we did not make any specific predictions, but rather treated the correlations as exploratory in nature.

4.3 Methods

4.3.1 Participants

Twenty-one MCI patients, 16 AD patients, and 26 normal elderly controls (NECs) were selected for inclusion in the final sample of the present study. The same participants used in two of our concurrent studies (Johns et al., 2015; Johns & Phillips, 2015a) were selected for this study in order to allow for direct comparison across studies. A general health questionnaire was administered to screen participants for neurological conditions other than MCI or AD, medical conditions that might affect cognition (e.g., uncontrolled thyroid dysfunction, B_{12} deficiency, alcohol abuse), and psychiatric disorders (other than mild depression). In addition, the Geriatric

Depression Scale (GDS; Yesavage et al., 1982) was administered, and any participant with a score greater than six was not admitted to this study. The Subjective Memory Complaints Scale (SMCS; Schmand et al., 1996) was also administered in order to characterize self-ratings of memory functioning. From the larger sample initially recruited for this study, two MCI patients, one AD patient, and seven NECs were excluded in order to generate a sample with identical participants to those used in the analysis of data collected for our concurrent studies (Johns et al., 2015; Johns & Phillips, 2015a). Reasons for exclusion included insufficient artifact-free epochs in any of the conditions, atypical task performance, technical errors during testing, or excessively noisy EEG recordings.

As reported elsewhere (Johns et al., 2015; Johns & Phillips, 2015a), MCI and AD participants were recruited and diagnosed at the Memory Clinic of the Sir Mortimer B. Davis–Jewish General Hospital (JGH), a tertiary care referral center of McGill University, Montreal. Their clinical evaluations included full medical, neuropsychological, and neuroradiological assessments. NECs were recruited from research participation databases at the Cognition, Aging, and Psychophysiology Laboratory at Concordia University and the Memory Clinic at the JGH. Written informed consent was obtained from all participants, who were compensated $10 per hour for their participation. Participants were tested at Concordia University and the Jewish General Hospital, and ethical approval for the study was obtained from both institutions involved.

4.3.1.1 MCI patients. A diagnosis of MCI was given based on agreed-upon criteria (Petersen et al., 2009; Winblad et al., 2004), which included a subjective report of cognitive decline (by either the individual or family), which was gradual and of at least 6 months duration, a documentation of objective cognitive impairment on neuropsychological testing (i.e., ±1.5 SD of age-appropriate norms), the absence of significant impairment in activities of daily living, and failure to meet the ADRDA-NINCDS criteria for dementia (McKhann et al., 1984), as determined by the assessing physician in the Memory Clinic. All MCI patients were amnestic, either demonstrating an impairment on measures of episodic memory alone or impairments in episodic memory plus other cognitive domains.

4.3.1.2 AD patients. A diagnosis of AD was given based on the ADRDA-NINCDS criteria for possible or probable AD (McKhann et al., 1984), which included an established progressive cognitive decline and the absence of any other disease capable of producing the dementia syndrome. Only participants who were deemed to be able to sign the consent form

without assistance were included in this study; thus, all AD patients had a mild to moderate level of cognitive impairment and no severe cases were included (average MoCA score = 19.3).

4.3.1.3 Normal elderly controls. NECs were screened for general cognitive function using the Montreal Cognitive Assessment (MoCA; Nasreddine et al., 2005), a cognitive screening tool that is sensitive to detecting MCI. NECs were excluded if they scored below 26 on this measure.

4.3.2 Materials and Procedure

All participants completed a neuropsychological testing session and an EEG testing session, and subset of participants also completed MRI and PiB scans. EEG was recorded while at rest (data presented in Johns et al., 2015), during the Go/No-go task (data presented in Johns & Phillips, 2015a), during the N-back task, and during one other executive functioning task (data not presented here). The procedures for the neuropsychological testing and neuroimaging acquisition and processing were identical to those reported by Johns et al. (2015), and are presented below.

4.3.2.1 Neuropsychological Testing. All participants completed a neuropsychological test battery administered according to standardized procedures and in a standardized order. The battery included measures of verbal abstract reasoning (Similarities subtest of the Wechsler Adult Intelligence Scale-Third Edition, WAIS-III; Wechsler, 1997), processing speed (Symbol Search subtest of the WAIS-III; Wechsler, 1997), short-term memory span (Digit Span subtest of the WAIS-III; Wechsler, 1997), confrontational naming (Boston Naming Test, 15-item version; Kaplan et al., 1983), verbal episodic memory (California Verbal Learning Test – Second Edition; Delis et al., 2000), working memory (Letter Number Sequencing subtest of the WAIS-III; Wechsler, 1997), phonemic and semantic verbal fluency (letters F, A, and S, and animals; Strauss et al., 2006), cognitive flexibility (Trail Making Test; Reitan, 1979; Strauss et al., 2006), and inhibitory control (Hayling Sentence Completion Test; Burgess & Shallice, 1997; and Victoria verion of the Stroop Test; Strauss et al., 2006).

4.3.2.2 EEG Recording. EEG was recorded during the performance of the N-back task, as well as while at rest (eyes-closed) for three minutes and during the performance of two other executive function tasks (data not presented here). The data were acquired using Neuroscan Acquire software (Neuroscan, 2003) from 32 Ag/AgCl electrodes mounted in an elastic Easycap and placed according to the International 10-20 system, with a bandpass of DC-100 Hz and a

sampling rate of 500 Hz. All sites were referenced to the left ear and re-referenced offline to linked ears. Electrode impedances were kept below 8 kΩ (and in most cases, below 5 kΩ). Electro-oculogram (EOG) activity was recorded supra-orbitally and from the outer canthi of both eyes in order to monitor eye movement, and corrected offline using ocular correction independent component analysis in BrainVision Analyzer 2.0 (*BrainVision Analyzer User Manual*, 2013).

4.3.2.3 Spectral analysis of EEG data. EEG data were processed offline using BrainVision Analyzer 2.0 software (*BrainVision Analyzer User Manual*, 2013). A DC drift correction and a 1-50 Hz phase shift-free Butterworth filter with a 12 db roll-off was applied to the continuous EEG files. EEG recorded during the N-back task was segmented in 1024 ms epochs beginning at the presentation of the stimulus for each trial. Segments containing deflections of greater than ±100 μV were excluded from further analysis. Data were transformed to the frequency domain using a fast Fourier transform (FFT) with a Hanning window. Average power and coherence were calculated for the following frequency bands: delta (1-3.5 Hz), theta (3.5-7.5 Hz), alpha (7.5-12.5 Hz), beta (12.5-30 Hz), and gamma (30-45 Hz).

4.3.2.4 Spectral Coherence Analysis. EEG coherence was calculated using the following formula for segment number i, fixed frequency f, and fixed channel c:

$$Coh(c_1, c_2)(f) = | CS(c_1, c_2)(f) |^2 / (| CS(c_1, c_1)(f) | | CS(c_2, c_2)(f) |),$$

where $CS(c_1, c_2)(f) = \Sigma\, c_{1,\,i}\,(f)\, c_{2,\,i}\,(f)$

The numerator contains the cross-spectrum of two EEG signals c_1 and c_2 ($CS(c_1, c_2)$) for a given frequency bin (f) and the denominator contains the autospectra for c_1 ($CS(c_1, c_1)$) and c_2 ($CS(c_2, c_2)$). The coherence value is equivalent to the squared complex correlation coefficient (Pfurtscheller & Andrew, 1999; Rappelsberger & Petsche, 1988), and coherence values range from 0 (no coherence) to 1 (maximal coherence). EEG coherence was computed for the following electrode pairs of interest: F3-F4, P3-P4, O1-O2, F3-P3, and F3-O1. These electrode pairs were chosen based on previous research that has implicated a fronto-parietal network underlying executive function, and the cross-hemisphere occipital pair and fronto-occipital pair were chosen for comparison to electrode pairs outside the fronto-parietal network. For the calculation of EEG coherence, the minimum number of segments was 24 for 0-back (M = 54.4), 21 for 1-back (M = 49.7), and 16 for 2-back (M = 37.8). A Fisher's Z transformation was

applied to the square root of coherence values in order to normalize the distribution for statistical analysis.

4.3.2.5 MRI acquisition & cortical thickness processing. Cortical thickness data were available for seven NECs, 17 MCI patients, and seven AD patients. MRI scans were acquired on a 1.5 Tesla Siemens Sonata Vision scanner at the Montreal Neurological Institute (MNI) and were done within one year of the EEG testing for MCI patients (M = 0.56 years) and within two years of EEG testing for NECs (M = 1.10 years) and AD patients (M = 1.21 years). High-resolution T1-weighted anatomical scans were obtained using a three-dimensional spoiled gradient echo sequence (T_R= 22ms; T_E= 9.2ms; flip angle= 30°; FOV = 256 x 256; 160 or 176 slices; 1-mm isotropic) along the sagittal plane.

MRI scans were processed using the automated CIVET pipeline (The McConnell Brain Imaging Centre, Montreal Neurological Institute). Briefly, tissue classification generated a gray and white matter surface for each subject, which was then aligned to a model surface. The difference in distance between the aligned gray and white matter surfaces was computed at each of 81924 vertices (40962 per hemisphere) using the *t-link* method, providing a measure (in mm) of cortical thickness at each of those vertices. Finally, thickness values were smoothed using a 20-mm surface smoothing filter. In order to permit analysis by region of interest (ROI), customized Automated Anatomical Labeling atlas (Tzourio-Mazoyer et al., 2002) labels were strongly warped (non-linearly) onto the subject's surface, yielding an individually-labeled surface with one label at each vertex. Next, the thickness vector file was matched against the newly created labels vector file, allowing for the computation of cortical thickness values for each ROI. The ROIs analyzed in the present study were chosen to sample frontal and parietal areas as a comparison for the EEG data as well as medial temporal areas, which are known to be affected in early AD. The five ROIs selected were the superior frontal gyrus, middle frontal gyrus, anterior cingulate cortex, superior parietal lobule, and parahippocampal gyrus (all in the left hemisphere).

4.3.2.6 PiB-PET acquisition and processing. PiB-PET data were available for 10 NECs, 13 MCI patients, and seven AD patients. Scans were acquired on a Siemens/CTI ECAT HR+ scanner in 3-dimensional imaging mode (63 parallel planes) at the MNI. All scans were done within one year of the EEG testing for MCI patients (M = 0.57 years) and within two years of EEG testing for NECs (M = 0.87 years) and AD patients (M = 1.08 years). Subjects were

scanned either for either 90 minutes immediately following injection of the [C-11]PiB bolus (34 frames collected) or for 40 minutes commencing 50 minutes after the injection (7 frames collected). The difference in scanning times was due to a need to shorten scan times after receiving feedback from participants that the scan time was too long.

The PiB volume was aligned to the participants' native anatomy according to the T1-weighted MRI scan. This was followed by registration of both native-space volumes to the MNI symmetrical template using a 12-parameter linear transformation. The resulting stereotactic-space dynamic volume was blurred with a 6-mmm full-width at half-maximum Gaussian filter in order to minimize the effects of random high-frequency spikes in the data and increase the signal-to-noise ratio. Blurring filter width was minimized in order to prevent the blurring of the signal within the cerebellar gray and white matter.

Ratio values were computed at each voxel using all seven frames collected during 40 minute scans and the last five frames collected during 90 minute scans (50 minutes post-injection, 40 minutes total scan time). First, the area under the curve (AUC) across time was computed for the cerebellar gray matter reference values, and at each voxel within the volume. Ratios were then computed by dividing each voxel's AUC value by the cerebellar gray AUC. Average PiB ratio values were computed for each ROI as defined by the Automated Anatomical Labeling atlas (Tzourio-Mazoyer et al., 2002). Consistent with the cortical region ROIs, the six ROIs that were analyzed in the present study were the superior frontal gyrus, middle frontal gyrus, anterior cingulate cortex, superior parietal lobule, hippocampus, and parahippocampal gyrus (all in the left hemisphere).

4.3.2.7 N-back task. The N-back task is a working memory (WM) task in which participants are required to continually maintain and update information held in mind. Single digits (1 through 9) were presented sequentially on a computer screen in white font on a black background (Arial 150 point font). Three levels of the N-back task were completed in ascending order of WM load (0-back, 1-back, 2-back). In each condition, the participant was required to indicate with a button press whether or not the current stimulus matched the stimulus presented *n* trials previously; in the 0-back task, participants were required to indicate whether the stimulus was a match to a fixed target number identified at the beginning of the block. Each condition consisted of 100 trials, of which 40% were match trials (match vs. non-match trials were distributed pseudorandomly). Each digit was presented an equal number of times, in a

pseudorandom order (constrained by the requirements of our match/non-match trial ratio). Stimuli were presented for 600 ms, with an inter-stimulus intervals of 1400 ms. Participants responded by pressing the left or right button on a keypad with the index finger of each hand. The designation of the left or right button as the match or non-match key was counterbalanced across participants. Before each condition, participants completed a brief practice block, which was repeated if necessary until the participant fully understood the task. Feedback for errors was given during the practice block in the form of an audible tone. Trials in which responses occurred less than 150 ms following the stimulus presentation or greater than 3 standard deviations longer than the participant's mean reaction time were excluded.

4.4 Results

Data for demographic characteristics, neuropsychological testing, cortical thickness, and PiB retention have been previously presented (Johns et al., 2015), and are summarized in Table 4.1. Briefly, there were no significant differences between groups in age, educational level, sex distribution, or depressive symptomatology. AD patients reported higher subjective memory complaints (SMCS) than NECs, and there was a trend for higher subjective memory complaints in MCI patients versus NECs. On the MoCA test, both AD patients and MCI patients scored lower than NECs, and AD patients also scored lower than MCI patients.

Neuropsychological testing was conducted in order to characterize the groups and verify the presence of deficits in executive functioning. Each neuropsychological test was analyzed with a separate univariate or multivariate analysis of variance (ANOVA), as appropriate. AD patients performed significantly worse than controls on a number of measures across several cognitive domains. These included verbal abstract reasoning (Similarities subtest), visual processing speed (Symbol Search), Digit Span forward, confrontational naming (Boston Naming Test), verbal episodic memory (CVLT total learning trials and delayed recall), working memory (Letter-Number Sequencing subtest), semantic and phonemic verbal fluency, and inhibitory control (errors on the Stroop test and errors on the Hayling test). MCI patients also performed significantly worse than controls on a number of measures, including verbal abstract reasoning (Similarities subtest), visual processing speed (Symbol Search), verbal episodic memory (CVLT total learning trials and delayed recall), semantic verbal fluency, and inhibitory control (Hayling test errors).

Cortical thickness and PiB retention were analyzed using separate multivariate ANOVAs. Cortical thickness was reduced in the parahippocampal gyrus in MCI and AD patients in comparison to controls and in the anterior cingulate cortex in AD patients (there was also a non-significant trend for reduced thickness of the anterior cingulate cortex in MCI patients). PiB retention was higher in AD patients in comparison to controls in the superior frontal gyrus, middle frontal gyrus, anterior cingulate cortex, and superior parietal lobule. In MCI patients, PiB retention was higher than that of controls in the superior frontal gyrus, and there were non-significant trends for higher PiB retention in the middle frontal gyrus and the anterior cingulate cortex.

4.4.1 Statistical Analysis

Statistical analysis was conducted using SPSS v.22.0 software. For analyses with more than one degree of freedom in the numerator, a Huynh and Feldt (1976) correction was used for violations of sphericity. In these cases, the unadjusted degrees of freedom, the adjusted *p*-value, and the Huynh-Feldt epsilon value (ε) are reported. In the following analysis of behavioural and EEG data for the N-back task, only correct non-match trials are considered. Non-match trials were selected for analysis because there was a greater number of non-match trials at each WM load (60 non-match trials vs. 40 trials match), allowing for a greater number of segments to be included in the analysis of the EEG data.

4.4.2 N-back Behavioural Results

Figure 1 depicts reaction time and accuracy on the N-back task, which were analyzed using separate two-way mixed design ANOVAs in order to examine the effects of group (AD, MCI, NEC) and WM load (0-back, 1-back, 2-back). As we expected that the MCI and AD groups would show deficits at different WM loads (i.e., that AD patients would show deficits at all WM loads and that MCI patients would only show a deficit on the 2-back), we conducted planned pairwise post-hoc comparisons between groups at each WM load. With regards to reaction time on the N-back task, the main effect of group was not significant, $F(2, 60) = 1.62$, $p = .207$, $\eta^2_p = .05$; however, there was a main effect of WM load, $F(2, 120) = 120.86$, $p < .001$, $\eta^2_p = .67$, $\varepsilon = .74$, such that reaction time increased with load (0-back < 1-back, $p < .001$; 1-back < 2-back, $p < .001$). Pairwise comparisons revealed that AD patients responded significantly more slowly than normal controls on the 1-back condition ($p = .041$).

Accuracy was calculated as a d' score in order to control for response bias (d' = z(correct hits ratio) – z(false positives ratio)). There was a significant main effect of WM load, F (2, 120) = 247.83, $p < .001$, $\eta^2_p = .81$, such that accuracy decreased with load (0-back > 1-back, $p < .001$; 1-back > 2-back, $p < .001$). There was also a significant main effect of group, $F(2, 60) = 11.51$, $p < .001$, $\eta^2_p = .28$, where AD patients performed significantly worse than both MCI patients ($p = .003$) and controls ($p < .001$), and MCI patients and controls did not differ significantly. Pairwise comparisons revealed that AD patients performed significantly worse than both MCI patients and controls for all levels of WM load ($p < .05$ in all cases), and MCI patients tended to show lower accuracy than NECs on the 2-back condition which just missed conventional levels of significance testing ($p = .056$), but did not differ from controls at lower WM loads (see Figure 4.1). It is important to note that, although the mean d' score for AD patients on the 2-back task was above chance levels, approximately half of the AD patients performed near chance (d' < 0.75) on this condition. Therefore, results for the 2-back condition in AD patients must be interpreted with caution due to the possibility that a number of AD patients in our sample may not have been engaged in the task for that condition.

4.4.3 Spectral EEG Power Analysis

Average power for each frequency band was measured for frontal (F3, Fz, F4), central (C3, Cz, C4), parietal (P3, Pz, P4), and occipital (O1, O2) electrode sites. The data were positively skewed; therefore, a logarithmic transformation was applied in order to normalize the distributions.

Mean power during the N-back task is presented in Figure 4.2. An omnibus 5 x 4 x 2 x 3 mixed design ANOVA was used to analyze spectral power for the N-back task in order to examine the effects of frequency band (delta, theta, alpha, beta, gamma), electrode site (frontal, central, parietal, occipital), WM load (0-back, 1-back, 2-back), and group (NEC, MCI, AD). There were no main effects of WM load, $F(2, 120) = 1.11$, $p = .218$, $\eta^2_p = .02$, or group, $F(2, 60) = 1.78$, $p = .178$, $\eta^2_p = .06$. There was a main effect of frequency band, $F(4, 240) = 545.54$, $p < .001$, $\eta^2_p = 0.90$, $\varepsilon = .588$, such that power was greatest in the delta band followed by theta, alpha, beta, and gamma ($p < .01$ in all cases).

There were significant interactions between frequency band and WM load, $F(8, 480) = 3.93$, $p = .010$, $\eta^2_p = 0.06$, $\varepsilon = .501$, and between frequency band, WM load, and site, $F(24, 1440)$

= 6.05, $p < .001$, $\eta^2_p = 0.09$, $\varepsilon = .297$. There was a marginally significant interaction between WM load and group, $F(4, 120) = 2.17$, $p = .100$, $\eta^2_p = 0.07$, $\varepsilon = .721$.

We conducted post-hoc comparisons with Least Significant Differences (LSD) tests in order to examine the effects of WM load and group specific to each frequency band (effects reported as significant are all $p < .05$).

4.4.3.1 Effect of working memory load. Pairwise comparisons revealed that the effect of WM load on power varied by frequency band. As can be seen in Table 4.2, for NECs, power tended to decrease with increasing WM load over central and parietal sites in the delta band and over all sites in the alpha band. MCI patients showed a similar decrease in alpha power with WM load at all sites, but also exhibited an increase in delta and theta power over frontal sites with increasing WM load. In contrast, AD patients failed to show a reduction in alpha power with WM load, but showed a reduction in beta and gamma power over frontal sites with increasing WM load (0-back to 1-back) and an increase in beta and gamma power over posterior sites with increasing load (1-back to 2-back). AD patients also showed a more widespread increase (i.e., involving both anterior and posterior regions) in delta and theta power with WM load.

4.4.3.2 Effect of group. Table 4.2 also summarizes group differences at each WM load. As can be seen in the table, MCI patients did not differ significantly from NECs; however AD patients showed reduced power for 0-back and 1-back in the delta, theta, alpha, and beta bands, mainly over posterior sites.

Overall, this pattern of results indicates that: (1) the EEG power during the WM task was largely characterized by lower frequencies, (2) alpha power decreased with WM load for NECs and MCI patients, but not for AD patients, (3) AD patients showed a pattern of decreased beta and gamma power with WM load over frontal sites, but increased beta and gamma power with load over posterior sites, (4) MCI patients exhibited an increase in delta and theta power with WM load over frontal sites, and AD patients showed a widespread increase in delta and theta power with WM load, and (5) in comparison to NECs, AD patients showed reduced power in the delta, theta, alpha, and beta bands mainly over posterior sites during the 0-back and 1-back tasks.

4.4.4 EEG Coherence

EEG coherence was analyzed for two separate families of electrode pairs: cross-hemisphere homologous pairs (F3-F4, P3-P4, O1-O2), and long distance intrahemispheric pairs

(F3-P3, F3-O1). Each set of analyses was performed in two steps. First, the effect of WM load was analyzed separately for each frequency band and group with repeated measures ANOVAs with WM load and electrode pair as the within-subjects factor. Second, the effect of group was analyzed separately for each frequency band and WM load and for the difference between 0-back and 1-back and between 1-back and two back. We analyzed the difference scores between WM loads in order to evaluate group differences in the change in coherence with increasing WM load. These analyses were conducted with mixed design ANOVAs with electrode pair as the within-subjects factor and group as the between-subjects factor.

4.4.4.1 Cross-hemisphere homologous pairs. The EEG coherence values obtained during the performance of the N-back task for cross-hemisphere homologous pairs are presented in Figure 4.3, and the subtraction values for the difference between 0-back and 1-back and between 1-back and 2-back are presented in Figure 4.4.

4.4.4.1.1 Effect of working memory load. The ANOVA results for effect of WM load for cross-hemisphere homologous pairs at each frequency band for each group are presented in Table 4.3. The interaction between WM load and electrode pair is presented when significant, and when the interaction was not significant, the significant main effect of WM load is reported, if applicable. To begin with, the pattern in NECs revealed an increase in coherence from 0-back to 1-back in the theta band (main effect). In the alpha band, there was a decrease in frontal coherence from 0-back to 1-back and an increase from 1-back to 2-back (see Figure 4.3, solid lines in the theta and alpha bands and Figure 4.4, solid bars in the first column for the theta and alpha bands). Interestingly, there was no effect of WM load in the theta or alpha bands for MCI or AD patients. Instead, both groups showed an increase in coherence in the delta band as a function of WM load. MCI patients showed an increase in frontal coherence from 0-back to 1-back (see Figure 4.3, dashed line in the delta band and Figure 4.4, grey bar in the first column for the delta band), and AD patients showed an increase in occipital coherence from 1-back to 2-back (see Figure 4.3, dotted line in the delta band and Figure 4.4, white bar in the second column for the delta band). Moreover, the AD patients showed an increase in gamma frontal coherence from 0-back to 2-back (see Figure 4.3, dotted line in the gamma band).

4.4.4.1.2 Group differences. The ANOVA results for group differences for cross-hemisphere homologous pairs at each frequency band are presented in Table 4.4. The interaction between group and electrode pair is presented when significant, and when the interaction was not

significant, the significant main effect of group is reported, if applicable. As shown in Figure 4.3, there were significant main effects of group in the lower frequency bands (delta, theta, alpha), in which coherence was lower for AD patients in comparison to MCI patients and NECs at all three WM loads. There were no significant differences between MCI patients and NECs at any WM load.

Given that we were interested in the change in coherence as a function of WM load, we also examined difference values between the 0-back and 1-back and between the 1-back and 2-back coherence values in order to determine whether there were group differences in their response to WM load. As can be seen in the first column of Figure 4.4, NECs showed a larger decrease in frontal alpha coherence from 0-back to 1-back in comparison to MCI patients. In addition, AD patients showed an overall greater decrease in coherence in the beta band from 0-back to 1-back in comparison to MCI patients, and there was and a non-significant trend in the same direction for AD patients in comparison to NECs (p = .082). AD patients also showed a smaller increase in occipital gamma coherence from 0-back to 1-back in comparison to both MCI patients and NECs.

The second column in Figure 4.4 shows the change in coherence from 1-back to 2-back. As can be seen in this figure, AD patients showed a greater increase in occipital delta coherence in comparison to both NECs and MCI patients, and NECs showed a larger increase in frontal beta coherence in comparison to MCI patients.

4.4.4.2 Long distance intrahemispheric pairs. The EEG coherence values obtained during the performance of the N-back task for intrahemispheric pairs (F3-P3, F3-O1) are presented in Figure 4.5, and the subtraction values for the difference between 0-back and 1-back and between 1-back and 2-back are presented in Figure 4.6. As we were interested specifically in the effects for the fronto-parietal electrode pair, and the frontal-occipital pair was included for comparison, we performed the analyses for these two pairs separately.

4.4.4.2.1 Effect of working memory load. The ANOVA results for effect of WM load for F3-P3 and F3-O1 at each frequency band are presented in Table 4.5. To first outline the pattern of results in NECs, we found that for F3-O1, coherence increased at the highest working memory load (2-back) in the theta, alpha, beta, and gamma bands (see Figure 4.5, solid lines and Figure 4.6, black bars). MCI and AD patients generally showed the same pattern, with the exception that the impact of WM was at 0-back to 1-back rather than at 1-back to 2-back in the

gamma band (see Figure 4.5, dashed and dotted lines and Figure 4.6, grey and white bars). MCI patients additionally showed an increase from 0-back to 1-back in the delta band and AD patients showed an increase from 1-back to 2-back in the delta band.

For the fronto-parietal electrode pair, NECs showed the same pattern as the fronto-occipital pair, with increased coherence for the 2-back condition in the theta, alpha, and beta bands (see Figure 4.5, solid lines and Figure 4.6, black bars). MCI patients also showed increased coherence for 2-back in the theta and alpha bands; however, in the beta and gamma bands, coherence increased at a lower WM load (from 0-back to 1-back; see Figure 4.5, dashed lines and Figure 4.6 grey bars). AD patients did not show an effect of working memory load for the fronto-parietal pair in any frequency band (see Figure 4.5, dotted lines and Figure 4.6, white bars).

4.4.4.2.2 Group differences. There were no significant group differences at any working memory load or for the difference between WM loads for the F3-O1 electrode pair; therefore, we focus the results presented below on the F3-P3 electrode pair. The ANOVA results for group differences for the F3-P3 pair are presented in Table 4.6. There were no group differences for fronto-parietal coherence at 0-back. For the 1-back load, the only significant difference was for lower coherence in AD patients in comparison to NECs in the delta band (see Figure 4.5, dotted line, top left panel). For the 2-back load, AD patients showed significantly lower coherence than MCI patients in the delta, theta, and alpha bands (see Figure 4.5, left column, top three panels).

We also examined difference scores between WM loads in order to determine whether there were group differences in the change in coherence with WM load. We found that MCI patients exhibited a greater increase in fronto-parietal beta coherence from 0-back to 1-back in comparison to both NECs and AD patients (see Figure 4.6, left column, beta band). In addition, AD patients failed to increase theta coherence from 1-back to 2-back (see Figure 4.6, right column, theta band).

4.4.5 Correlational Analysis

In order to examine the relationship between the various neuroimaging measures and between the neuroimaging measures and measures of cognitive performance, we computed several exploratory Pearson correlations. We chose to examine EEG coherence for the difference between the 1-back and 0-back conditions, as this represents the change in coherence with the addition of a working memory component that is not too challenging for patients (i.e.,

AD patients perform above chance levels on the 1-back condition, but a subset of AD patients perform near chance on the 2-back condition). We also selected the electrode pairs of primary interest in the fronto-parietal network (F3-F4, P3-P4, F3-P3). We ran two sets of correlational analyses: (1) intercorrelations between neuroimaging measures for ROIs within frontal and parietal areas, and (2) correlations between neuroimaging measures and performance on the N-back task. We consider these data to be exploratory in nature due to the large number of correlations computed as well as the small sample size. As we were interested in exploring the relationship between these various measures in each of the individual groups, the sample size for the correlations is often quite small (e.g., $n = 7$ for any correlations with cortical thickness or PiB retention values for AD patients; refer to sample sizes presented in Table 4.1). Nevertheless, several significant correlations emerged in our examination of the data.

4.4.5.1 EEG coherence, cortical thickness, and PiB retention. First, we examined the relationship between EEG coherence (i.e., the difference between the 1-back and 0-back conditions) and both cortical thickness and PiB retention. A summary of the reliable correlations is presented in Table 4.7. From this table, it can be seen that overall, there were more significant correlations for AD and MCI patients than for NECs. In addition, in normal controls, there were reliable correlations between EEG coherence and PiB retention, but no reliable correlations between for EEG coherence and cortical thickness.

4.4.5.1.1 N-back EEG coherence and cortical thickness. EEG coherence was not reliably associated with cortical thickness in normal controls. In contrast, MCI patients showed a reliable association between lower cortical thickness and a smaller increase in frontal and fronto-parietal coherence, but a greater increase in parietal coherence. There was also a consistent pattern in the association between EEG coherence and cortical thickness in AD patients. In general, lower cortical thickness was associated with a smaller increase in cross-hemisphere coherence from 0-back to 1-back (theta, beta, and gamma bands).

4.4.5.1.2 N-back EEG coherence and PiB retention. An interesting pattern of results was obtained with respect to EEG coherence and PiB retention. First, the increase in frontal gamma coherence was reliably positively correlated with PiB retention for normal controls. In contrast, for MCI patients, the increase in parietal gamma coherence was negatively correlated with PiB retention. Sample scatterplots for correlations between EEG coherence and PiB retention in the for MCI patients and NECs are presented in Figure 4.7. Thus, in normal controls,

higher PiB retention in the anterior cingulate cortex and superior parietal lobule was associated with a greater increase in cross-hemisphere frontal gamma coherence, whereas in MCI patients, higher PiB retention in the prefrontal cortex and parietal cortex was associated with a smaller increase in cross-hemisphere parietal gamma coherence. Finally, in AD patients, higher PiB retention was associated with a smaller increase in coherence (frontal alpha with superior frontal gyrus and fronto-parietal delta with middle frontal gyrus). Thus, there was an overall pattern where the between PiB retention and EEG coherence increase was positive for NECs, but negative for AD and MCI patients.

4.4.5.2 Neuroimaging and N-back performance. The relationships between neuroimaging (EEG coherence, cortical thickness, and PiB retention) measures and performance on the 1-back condition are presented in Table 4.7. In NECs, there were no reliable associations between neuroimaging measures and N-back performance, and in MCI patients, there was no consistent pattern in the relationship between coherence and behavioural performance. In AD patients, however, lower accuracy was reliably associated with a greater increase in coherence (frontal delta and gamma and fronto-parietal alpha). In addition, higher RTs were also associated with a greater increase coherence (frontal delta and beta and fronto-parietal gamma). Thus, poorer accuracy and longer RTs were associated with a greater increase in frontal and fronto-parietal coherence.

With respect to the relationship between N-back performance and cortical thickness and PiB retention, the only significant association was for MCI patients, where higher PiB retention in the superior parietal lobule was associated with lower 1-back accuracy.

4.5 Discussion

The main goal of the present study was to examine EEG coherence during the performance of a working memory task in MCI and AD. We examined EEG coherence within a fronto-parietal network during the performance of an N-back task of working memory. We were also interested in exploring the relationship between EEG coherence and measures of brain integrity (cortical thickness and PiB retention), as well as between these neuroimaging measures and performance on the N-back task; therefore, we conducted a number of exploratory correlations to examine these relationships. Results are summarized and discussed below.

4.5.1 Group Differences on Cognitive Measures

We conducted neuropsychological testing in order to confirm the presence of deficits in executive functioning in our sample of MCI and AD patients. In addition to deficits on tests of verbal abstract reasoning, visuomotor processing speed, short-term memory span, confrontational naming, and verbal episodic memory, AD patients showed deficits on tests of executive functioning including working memory, semantic and phonemic verbal fluency, and inhibitory control. MCI patients also exhibited deficits on tests of executive functioning, including measures of semantic verbal fluency and inhibitory control. Other areas of impairment in MCI patients included verbal abstract reasoning, visual processing speed, and verbal episodic memory. On the neuropsychological test of working memory (Letter-Number Sequencing), AD patients performed significantly worse than controls, and there was a tendency towards lower performance in MCI patients in comparison to controls.

Importantly, on the n-back task, our experimental measure of working memory during which we recorded EEG, we saw the typical effect of working memory load where reaction time increased and accuracy decreased with load for all groups. Furthermore, AD patients demonstrated the lowest accuracy, with significantly reduced accuracy in comparison to normal controls for all working memory loads, and MCI patients exhibited lower accuracy in comparison to normal controls for the highest working memory load (2-back). This is consistent with previous literature (e.g., Borkowska et al., 2009; Lim et al., 2008; Rombouts et al., 2005).

4.5.2 EEG Coherence: Effect of Working Memory Load

In order to determine whether EEG coherence is affected by the manipulation of working memory load, we examined changes in coherence with load for the three groups. We found that coherence within a fronto-parietal network was modulated by working memory load in all groups, though the effect of working memory load varied across group, electrode pair, and frequency bands. In normal controls, interhemispheric coherence increased with working memory load in the theta band from 0-back to 1-back and frontal coherence decreased from 0-back to 1-back and increased from 1-back to 2-back in the alpha band (see Figures 4.3 and 4.4). Fronto-parietal coherence increased for the highest working memory load in the theta, alpha, and beta bands, whereas in the delta band, there was a decrease (see Figures 4.5 and 4.6).

Few previous studies have examined EEG coherence during a task with increasing memory load. However, in one study with young adults, fronto-parietal theta coherence was

modulated by memory load in a modified Sternberg task (Payne & Kounios, 2009). In addition, alpha coherence has been shown to decrease in working memory conditions in comparison to control conditions (Mizuhara et al., 2005; Sauseng et al., 2005). Furthermore, in a study that examined the effects of increasing working memory load during a mental arithmetic task in a group comprised of healthy older adults and MCI patients, EEG coherence was modulated by working memory load in all frequency bands examined (delta, theta, alpha, and beta), for interhemispheric electrode pairs as well as for intrahemispheric pairs. However, when compared to the resting condition, coherence decreased at the lowest memory load, and increased only for the highest load (Jiang et al., 2008). Our results cannot be directly compared to these studies due to differences in the task used as well as the participant groups examined. Nevertheless, our results are generally consistent with these previous studies, in that coherence increases at higher loads during a working memory task, across multiple frequency bands, and particularly for intrahemispheric pairs, and frontal alpha coherence decreases with the addition of a working memory load.

In contrast to normal controls, who showed a modulation of EEG coherence with working memory load in the theta and alpha bands, MCI patients and AD patients showed an effect of working memory for cross-hemisphere pairs in a lower frequency band (delta band). For MCI patients, frontal coherence increased from 0-back to 1-back, and for AD patients, occipital delta coherence increased from 1-back to 2-back (see Figures 4.3 and 4.4). For intrahemispheric pairs, MCI and AD patients showed a similar pattern as seen in normal controls for the fronto-occipital pair, and additionally showed increases in fronto-occipital coherence with working memory load in the delta band (see Figures 4.5 and 4.6). In contrast, MCI and AD patients showed a different pattern for the fronto-parietal pair. In AD patients, there was no modulation of fronto-parietal coherence with working memory load (see Figures 4.5 and 4.6), which could be indicative of a failure to recruit the fronto-parietal network during the performance of this working memory task. MCI patients, on the other hand, showed increased fronto-parietal coherence for the 2-back condition in the theta and alpha bands, similar to the pattern seen in normal controls; however, fronto-parietal coherence in higher bands (beta and gamma) increased at a lower working memory load (from 0-back to 1-back; see Figures 4.5 and 4.6). This is an interesting difference between MCI patients and normal controls, and may reflect that the 1-back task was more neurally demanding for MCI patients, despite preserved

behavioural performance. Thus, the increase in coherence may be compensatory, enabling MCI patients to maintain good performance on this task. Normal controls, on the other hand, show an increase in coherence from 1-back to 2-back, which could indicate that the cognitive effort, and thus the need for increased coherence, comes into play at a higher load. In AD patients, there is no consistent effect of working memory load on EEG coherence, which could be due to difficulties at all levels of the task.

4.5.3 EEG Coherence: Group Differences

4.5.3.1 Alzheimer's disease. Turning now to the results for group differences in EEG coherence during the performance of the N-back task, AD patients showed reduced cross-hemisphere coherence for all working memory loads in the lower frequency bands (delta, theta, alpha, see Figure 4.3). Furthermore, AD patients showed less of an increase in cross-hemisphere coherence from 0-back to 1-back in the beta band, and less of an increase in occipital coherence from 0-back to 1-back in the gamma band (see Figure 4.4). AD patients also showed lower fronto-parietal delta coherence during the 1-back condition (see Figure 4.5), and less of an increase in fronto-parietal theta coherence from 1-back to 2-back (see Figure 4.6). No previous studies have examined EEG coherence in AD during the performance of the N-back task; however, two studies have examined EEG coherence during short-term memory tasks. In one study, averaged central and averaged centro-temporal coherence measures were examined during a Sternberg task, and AD patients exhibited decreased coherence only for centro-temporal alpha coherence (Hogan et al., 2003). In the second study, a visual short-term memory task was used and synchronization likelihood was calculated for each electrode with all other electrodes and then averaged together. AD patients were compared to older adults with subjective memory complaints, and AD patients showed reduced mean coherence in the alpha and beta bands (Pijnenburg et al., 2004). Thus, no previous studies have examined cross-hemisphere or fronto-parietal coherence in AD patients during a short-term memory or working memory task, and our findings of reductions in coherence in these electrode pairs are novel. Our results suggest that cross-hemisphere coherence in the lower frequency bands is most strongly affected in AD patients during the performance of a working memory task. Additionally, fronto-parietal delta coherence is reduced, and coherence in cross-hemisphere electrode pairs in the higher frequency bands as well as in fronto-parietal electrode pairs in the theta band is less responsive to increasing task demands in AD patients.

The results of the present study can be directly compared to our two concurrent studies that used the same participants to examine EEG coherence while at rest (Johns et al., 2015) and during a task of inhibitory control (Johns & Phillips, 2015a). In these studies, we found that AD patients demonstrated reduced cross-hemisphere parietal coherence in the delta and theta bands while at rest, with no further reductions in coherence during sustained attention trials during the inhibitory control task. However, during inhibition trials, AD patients exhibited an additional reduction in cross-hemisphere frontal theta coherence in comparison to normal controls. In the present study, AD patients demonstrated reduced cross-hemisphere frontal, parietal, and occipital coherence for all working memory loads in the delta, theta, and alpha bands. Thus, overall, AD patients demonstrate reduced cross-hemisphere coherence while at rest and during the performance of executive functioning tasks in the lower frequency bands. However, only parietal coherence is reduced when at rest, and only frontal theta coherence is additionally reduced during the performance a task of inhibitory control. During a working memory task, reductions in coherence are more widespread, encompassing more electrode pairs (frontal, parietal, and occipital), and can be seen in more frequency bands (delta, theta, alpha).

4.5.3.2 Mild cognitive impairment. With regards to the group differences between MCI patients and controls, there were no EEG coherence differences between groups at any of the working memory loads (see Figures 4.3 and 4.5); however, the groups differed their pattern how coherence changed as a function of WM load. MCI patients exhibited a smaller decrease in coherence from 0-back to 1-back for frontal alpha (see Figure 4.5) and a greater increase in coherence from 0-back to 1-back for fronto-parietal beta (see Figure 4.6). In addition, MCI patients showed less of an increase in frontal beta coherence from 1-back to 2-back, which coincides with their drop in behavioural performance. Therefore, the greater increase in coherence from 0-back to 1-back may be compensatory in nature, allowing MCI patients to maintain good task performance. In contrast, their failure to increase coherence to the same degree as normal controls from 1-back to 2-back could reflect either inefficient recruitment of the frontal network causing poor behavioural performance, or that MCI patients have reached their working memory capacity at this level and that some other mechanism (such as task disengagement) results in reduced recruitment of the frontal network.

No previous studies have examined EEG coherence during the N-back task in MCI patients; however there have been studies that examined EEG coherence or synchronization

during the performance of short-term memory and working memory tasks. The studies that examined short-term memory tasks reported increased mean coherence in the alpha band (Pijnenburg et al., 2004) and increased cross-hemisphere frontal synchronization in the alpha and beta bands as well as increased cross-hemisphere anterior and posterior synchronization in the gamma band (Bajo et al., 2010). In the set of studies that examined coherence during a working memory task (Jiang, 2005b; Jiang et al., 2008; L.-L. Zheng et al., 2007), MCI patients exhibited a widespread increase in coherence across frequency bands, electrode pairs, and working memory loads. Furthermore, in our concurrent study using the same participants as the present study, fronto-parietal coherence was increased in MCI patients during the performance of a task of inhibitory control (Johns & Phillips, submitted). In the present study, we did not find increased coherence in MCI patients at any working memory load; however, MCI patients did show less of a decrease in coherence with working memory load for the cross-hemisphere frontal pair (alpha) and a greater increase in coherence the fronto-parietal pair (beta). It is difficult to directly compare the results of the present study to previous studies due to differences in the method of calculating synchronization, the type of task, and participant characteristics; however, our results can be viewed as generally consistent with previous findings of increased coherence in MCI patients, as well as with fMRI studies that have found increased activation in MCI patients during the performance of executive function tasks (e.g., Clément et al., 2013), which may represent a compensatory mechanism in MCI patients.

4.5.4 Correlational Analysis

4.5.4.1 Relationships between EEG coherence and neuropathology. In order to determine whether the change in coherence with working memory load was related to measures of brain integrity, we computed a number of correlations between the change in EEG coherence from 0-back to 1-back and measures of cortical thickness and PiB retention within frontal and parietal regions. The relationship between the change in EEG coherence and cortical thickness was variable across the three groups. First, there was no relationship between coherence and cortical thickness in normal controls; however, in MCI patients, less thickness in the prefrontal cortex and parietal cortex was associated with less of a working memory-driven increase in frontal theta and alpha coherence, but a greater increase in parietal theta coherence. In AD patients, lower cortical thickness was generally associated with a smaller increase in frontal and

parietal coherence. Thus, one pattern that can be seen from this data is that, in AD and MCI patients, cortical thickness appears to be primarily related to cross-hemisphere coherence.

To compare these results with our concurrent studies using the same participants, we found no consistent relationship between cortical thickness and EEG coherence at rest in any of the groups (Johns et al., 2015). Thus, it is interesting that in MCI and AD patients, cortical thickness was related to the change in EEG coherence during the performance of the N-back task, but not to resting coherence. Furthermore, in our study of inhibitory control, we found that cross-hemisphere parietal coherence (difference between inhibition and control trials) was positively associated with prefrontal cortical thickness in AD patients, but negatively associated with prefrontal and parietal thickness in MCI patients (Johns & Phillips, 2015a). Similarly, in the present study, the change in coherence from 0-back to 1-back was positively associated with cortical thickness (parietal cortex) in AD patients and negatively associated with thickness (frontal and parietal) in MCI patients. Thus, we have converging findings of an inverse relationship between cortical thickness and parietal coherence in MCI and AD patients during the performance of another executive task, and this increased parietal coherence with decreasing cortical thickness may represent a mechanism of compensation for atrophy in frontal and parietal cortical regions.

Turning now to the correlations between change in EEG coherence during the N-back task and PiB retention, the overall pattern indicated that higher PiB retention was associated with a greater increase in cross-hemisphere frontal gamma coherence in normal controls, but a smaller increase in coherence in MCI and AD patients (parietal gamma coherence in MCI patients and fronto-parietal delta and frontal alpha coherence in AD patients). Thus, with increasing amyloid burden, normal controls show a greater increase in coherence with working memory load, whereas patients show a smaller increase. Previous research has shown that PiB retention is significant (i.e., surpassing a specified threshold) in a minority of healthy elderly individuals (up to approximately 20%; Berti et al., 2010). It is possible that the positive association between amyloid burden and coherence increase in normal controls reflects a compensatory process in which cross-hemisphere frontal connectivity is successfully increased to compensate for amyloid deposition, which may help to support normal cognitive function. In contrast, the negative association between amyloid burden and parietal coherence increase in MCI patients may reflect that MCI patients are no longer able to make use of this compensatory process and that at this

stage in the illness amyloid burden has a negative impact on cross-hemisphere parietal connectivity. Future studies using longitudinal designs would be required to test this hypothesis.

To compare these results for PiB retention to our concurrent studies, the relationship between EEG coherence and PiB retention in the three groups was variable depending on whether coherence was measured at rest, during a task of inhibitory control, or during a task of working memory. Specifically, normal controls showed a positive relationship between PiB retention and fronto-parietal coherence at rest, but not during the performance of the Go/No-go task or N-back task. In addition, there was a negative relationship between PiB retention and cross-hemisphere frontal and parietal coherence at rest and during the Go/No-go task, but a positive relationship between PiB retention and cross-hemisphere frontal coherence during the N-back task.

In MCI patients, there was a consistent negative relationship between PiB retention and cross-hemisphere frontal and intrahemispheric fronto-parietal coherence at rest. The relationship between PiB retention and coherence during the N-back task was also negative, but the reliable association was with cross-hemisphere parietal coherence. In contrast, there was a positive relationship between PiB retention and cross-hemisphere parietal coherence during the Go/No-go task.

In AD patients, there was no reliable relationship between PiB retention and resting coherence, but PiB retention was negatively associated with frontal and fronto-parietal coherence during both the Go/No-go task and N-back task.

Thus, taken together, there is some evidence for a possible compensatory mechanism (higher PiB retention associated with higher coherence) in normal controls and MCI patients during the performance of a cognitive task, but this pattern is seen for the N-back task for normal controls and for the Go/No-go task for MCI patients. The relationship between PiB retention and functional connectivity is clearly complex and dependent upon diagnostic group, whether coherence is measured at rest or during the performance of a cognitive task, the type of cognitive task being performed, and the electrode pairs and frequency bands examined. In AD patients, in whom amyloid deposition is sufficiently advanced, higher amyloid deposition is consistently related with lower EEG coherence (i.e., no attempts at functional compensation); however, the pattern is variable in MCI patients and NECs, and is suggestive of compensatory processes under certain conditions.

4.5.4.2 Relationships between neuroimaging measures and N-back performance.

We also examined the relationship between behavioural performance on the 1-back task and change in EEG coherence from 0-back to 1-back, cortical thickness, and PiB retention. There were few significant correlations between neuroimaging measures and performance on the 1-back task. However, the strongest relationship emerged for AD patients, where frontal (delta, beta gamma) and fronto-parietal (alpha, gamma) coherence change was negatively correlated with 1-back accuracy and positively correlated with 1-back RT. The lack of a stronger relationship in normal controls and MCI patients between EEG coherence during the N-back task and performance on the task is surprising, as one would expect brain functioning during a task to be related to task performance. However, it is possible that the relationship between EEG coherence and cognition is more complex than a simple linear relationship between the two variables. Other factors, such as neurocognitive reserve, neuropathological burden, task strategies, and/or the use of potential compensatory mechanisms may play a role in moderating the relationship between coherence and cognition.

4.5.5 Implications

The present study makes several important contributions to our understanding of working memory abilities in AD and MCI patients. First, we confirmed the presence of deficits working memory in both patient groups, as measured by the Letter-Number Sequencing test and the N-back task. Second, we measured EEG coherence during the performance of the N-back task, and found that working memory load modulated EEG coherence within a network of frontal and parietal electrode pairs in the three groups. Importantly, the change in EEG coherence with working memory load varied across the three groups. In normal controls, changes in working memory load resulted in changes in coherence in frontal (theta and alpha), parietal (theta), and fronto-parietal (delta, theta, alpha, and beta) electrode pairs. In MCI patients, changes in working memory load resulted in coherence changes in cross-hemisphere frontal (delta), and fronto-parietal (theta, alpha, beta, and gamma) electrode pairs. In AD patients, coherence was modulated by working memory load only for the cross-hemisphere frontal electrode pair in the gamma band. Thus, there appears to be changes in the way that working memory load modulates EEG coherence in MCI patients versus controls, though a fronto-parietal network is still activated during the performance of the task. In contrast, AD patients did not show

modulation of the fronto-parietal electrode pair with working memory load, which may indicate a failure of connectivity within this network.

A third important implication of the present study is that we found that there are group differences on EEG coherence measures during the performance of a working memory task that are not present while at rest (Johns et al., 2015). Thus, there are alterations in functional connectivity within a fronto-parietal network in both AD and MCI patients that may be detectable only when performing a task that taps into frontal lobe functions. Our results also suggest that changes in functional connectivity are different depending on the stage of the disease. While AD patients demonstrate reduced cross-hemisphere functional connectivity in the lower frequency bands and less of an increase in fronto-parietal coherence from 1-back to 2-back, MCI patients show altered functional connectivity only in the change in coherence with working memory load. Thus, while MCI patients recruit a greater increase in connectivity within a fronto-parietal network to support working memory at lower loads, this process breaks down at higher working memory loads and at more advanced stages of the illness.

Furthermore, these results suggest that valuable information may be gained from exploring how EEG coherence changes with task demands. EEG coherence appeared to be similar in MCI patients and controls during the performance of the N-back task, but the examination of the changes in coherence with working memory load revealed that MCI patients may be recruiting additional neural resources at a lower level of task difficulty despite similarities in performance. This suggests the importance of measuring EEG coherence during various states including a resting state and various levels of cognitive performance.

Finally, though the intercorrelations between neuroimaging measures and correlations between neuroimaging measures and measures of cognition were exploratory in nature and produced somewhat mixed results in the present study, several interesting patterns emerged that warrant further investigation. In particular, the correlational analysis highlights the complexity of the relationship between brain functioning, neuropathology, and cognition. The relationship between these variables differs in each of the groups and depending on whether EEG coherence was measured at rest or during cognitive performance. The data suggest some specific relationships between neuroimaging measures (e.g., a relationship between neuropathology and cross-hemisphere but not intrahemispheric coherence in AD and MCI patients), some possible compensatory mechanisms (e.g., increased parietal coherence with decreasing cortical thickness

in MCI patients), and a stronger relationship between neuropathology and EEG coherence when coherence is measured during cognitive performance. It is interesting to note that while working memory load modulated both frontal and fronto-parietal coherence in MCI patients, it was primarily cross-hemisphere coherence that was significantly related to PiB retention and cortical thickness in this group (most notably cross-hemisphere parietal coherence). Our interpretation of the correlational analysis is limited by the small sample size, but future studies should help to elucidate the relationships between these factors.

4.5.6 Strengths and Limitations

This is the first study to examine EEG coherence during the performance of an N-back task in patients with AD and MCI. A major strength of the study is the use of a well-validated working memory task, tapping into a cognitive domain that is known to be affected in MCI and AD. This is also the first study to directly examine the relationships between EEG coherence during a working memory task and cortical thickness and PiB retention in AD and MCI patients. However, the small sample size for the correlational analysis, particularly for cortical thickness and PiB retention for AD patients and controls, limited our ability to draw strong conclusions from the correlational analysis and to use more sophisticated statistical techniques. For example, we did not find any significant correlations between cortical thickness and EEG coherence in normal controls. This could be due the relatively small variation in cortical thickness in controls; however, it is also possible that we lacked statistical power to detect significant associations.

Another limitation of the present study is that there was a time delay between the measurement of EEG coherence and neuropathology (cortical thickness and PiB), due to practical constraints. As MRI and PiB scans were performed within one year of EEG testing for MCI patients and within two years of EEG testing for normal controls and AD patients, it is possible that neuropathological changes occurred between the two testing sessions, which could have affected correlations between these variables. In future studies that examine the relationship between neuropathology and EEG coherence, it would be beneficial to obtain neuropathological measures closer in time to measures of EEG coherence. Finally, it is important to note that, as the EEG signal is known to be affected by multiple generators, we cannot be exact about which specific brain regions give rise to the signal recorded at a particular electrode site. Though we have assumed that activity recorded at frontal sites reflects primarily

frontal cortical activity, and activity recorded at parietal sites reflects primarily parietal cortical activity, we cannot be more specific about the localization of the signal generated.

4.5.7 Conclusions and Future Directions

Overall, the results from the present study point to altered functional connectivity within a fronto-parietal network during the performance of a working memory task in both AD and MCI patients. In particular, AD patients exhibited reduced cross-hemisphere functional connectivity during task performance in the lower frequency bands, and MCI patients exhibited altered changes in coherence with working memory load in the alpha and beta bands. Thus, AD patients experience difficulty with the task at all working memory loads, which is reflected by lower cross-hemisphere coherence across working memory loads. In contrast, behavioural performance is relatively preserved during the 0-back and 1-back tasks in MCI patients, and a greater recruitment of frontal and fronto-parietal connectivity from 0-back to 1-back may support preserved 1-back performance, whereas a smaller increase in coherence from 1-back to 2-back may be related to the drop in performance in the 2-back condition.

The interpretation of the relationships between EEG coherence and other neuropathological and cognitive variables is difficult due to individual differences in the stage of the illness, level of cognitive functioning, neurocognitive reserve, the use of compensatory mechanisms, and whether neural compensation mechanisms are successful or unsuccessful. Longitudinal studies in which changes within subjects are examined over the course of progression from normal cognitive function to dementia would be useful in addressing some of these issues. The relationships between these factors may be further elucidated by studies that examine the effects of pharmacological treatments and cognitive interventions on EEG coherence and cognition.

Table 4.1.

Summary Data for Demographics, Clinical Screening Tests, Neuropsychological Test Scores, Cortical Thickness, and PiB Retention

	NEC			MCI			AD			Group
Variable	***n***	***M***	***SD***	***n***	***M***	***SD***	***n***	***M***	***SD***	**Differences[a]**
Demographics										
Age	26	78.2	4.4	21	80.2	5.7	16	79.7	5.5	n.s.
Education	26	14.4	4.0	21	13.7	4.1	16	13.8	2.9	n.s.
Sex (% Female)	26	57.7	--	21	52.4	--	16	25.0	--	n.s.
Screening Tests										
GDS	26	1.4	1.7	21	1.6	1.7	16	2.0	1.7	n.s.
SMCS	26	3.1	2.7	21	4.7	2.4	16	6.8	5.4	AD>NEC
MoCA	26	27.6	1.5	21	22.5	4.3	16	19.3	4.3	AD<MCI<NEC
Neuropsychological Tests										
Similarities (Total /33)	26	24.5	4.4	21	19.1	4.3	16	17.4	6.6	AD=MCI<NEC
Symbol Search (Total /60)	26	25.4	5.4	19	19.5	7.3	16	13.9	9.2	AD<MCI<NEC
Digit Span Forward (Total /16)	26	6.6	1.2	11	5.6	1.6	14	5.1	0.9	AD<NEC[b]
Digit Span Backwards (Total /14)	26	5.1	1.4	11	4.1	1.3	14	4.1	0.9	n.s.[c]
Boston Naming Test (Total /15)	26	13.7	1.5	21	12.3	3.7	16	8.9	3.5	AD<MCI=NEC
CVLT Total Learning Trials (max /80)	26	46.0	7.0	21	30.8	8.2	16	22.2	7.2	AD<MCI<NEC
CVLT Long Delay (max /16)	26	10.3	3.2	21	3.9	3.6	16	1.3	1.9	AD<MCI<NEC
Letter Number Sequencing (Total /21)	26	9.9	3.0	12	8.1	1.7	12	6.6	3.2	AD<NEC[b]
Phonemic Fluency (Total Words: FAS)	25	42.5	10.9	20	36.2	11.8	16	29.8	12.5	AD<NEC
Semantic Fluency (Total Words: Animals)	25	17.8	4.1	20	12.7	4.3	16	9.1	4.3	AD<MCI<NEC
Trail Making Test Time in sec. (B/A)	22	2.8	1.5	14	2.8	1.1	14	4.0	2.9	n.s.[c]
Stroop Victoria Time in sec. (Colour/Dots)	26	1.8	0.5	13	2.2	0.7	14	2.1	0.5	n.s.
Stroop Victoria Errors (Colour - Dots)	26	0.1	0.4	13	1.7	2.1	14	2.6	4.3	AD>NEC
Hayling Test Time in sec. (Condition 2/1)	25	8.3	6.7	18	8.9	6.3	14	4.6	8.8	n.s.
Hayling Test Errors Scaled Score[d]	25	7.0	1.6	18	4.9	2.6	14	4.1	2.7	AD=MCI<NEC
Hayling Test Total Scaled Score	25	5.8	1.4	18	4.4	1.9	14	2.2	1.6	AD<MCI<NEC
Cortical Thickness										
Superior frontal gyrus	7	3.04	0.2	17	2.92	0.2	7	2.82	0.2	n.s.
Middle frontal gyrus	7	2.99	0.2	17	2.85	0.2	7	2.85	0.2	n.s.
Anterior cingulate cortex	7	3.63	0.2	17	3.45	0.2	7	3.39	0.2	AD<NEC[b]

Superior parietal lobule	7	2.67	0.3	17	2.57	0.2	7	2.60	0.2	n.s.
Parahippocampal gyrus	7	3.45	0.1	17	3.25	0.2	7	2.93	0.1	AD<MCI<NEC
PiB Retention										
Superior frontal gyrus	10	1.06	0.1	13	1.35	0.4	7	1.42	0.3	AD, MCI>NEC
Middle frontal gyrus	10	1.13	0.2	13	1.40	0.4	7	1.52	0.3	AD>NEC[b]
Anterior cingulate cortex	10	1.44	0.2	13	1.79	0.6	7	1.90	0.4	AD>NEC[b]
Superior parietal lobule	10	1.15	0.2	13	1.33	0.5	7	1.54	0.3	AD>NEC
Hippocampus	10	1.39	0.1	13	1.46	0.2	7	1.31	0.1	AD<MCI
Parahippocampal gyrus	10	1.19	0.1	13	1.26	0.2	7	1.21	0.1	n.s.

Note. Due to a change in the procedure for the administration of the neuropsychological test battery at the memory clinic during the period of data collection for this study, certain neuropsychological tests are missing data for several participants, as indicated in the table above. NEC = normal elderly controls; MCI = mild cognitive impairment; AD = Alzheimer's disease; GDS = Geriatric Depression Scale; SMCS = Subjective Memory Complaints Scale; MoCA = Montreal Cognitive Assessment; CVLT = California Verbal Learning Test. [a]Group differences noted in this column are at a significance level of $p < .05$. [b]$p < .10$ for MCI<NEC. [c]$p < .10$ for AD<NEC. [d]Higher scores indicate better performance.

Table 4.2.

Spectral EEG Power Analysis: Effects of Working Memory Load and Group

	Effect of Working Memory Load			Effect of Group		
	NEC	MCI	AD	0-back	1-back	2-back
Delta						
Frontal	n.s.	0-back<1-back=2-back	0-back=1-back<2-back	n.s.	n.s.	n.s.
Central	0-back>1-back=2-back	n.s.	n.s.	AD<NEC	AD<MCI=NEC	n.s.
Parietal	0-back>1-back>2-back	n.s.	1-back<0-back=2-back	AD<NEC	AD<NEC	n.s.
Occipital	n.s.	n.s.	0-back=1-back<2-back	AD<NEC	n.s.	n.s.
Theta						
Frontal	n.s.	0-back<1-back	0-back<2-back	n.s.	n.s.	n.s.
Central	n.s.	n.s.	1-back<2-back	n.s.	n.s.	n.s.
Parietal	n.s.	n.s.	1-back<2-back	n.s.	n.s.	n.s.
Occipital	n.s.	n.s.	0-back=1-back<2-back	n.s.	AD<NEC	n.s.
Alpha						
Frontal	0-back>1-back=2-back	0-back>1-back	n.s.	n.s.	n.s.	n.s.
Central	0-back>2-back	0-back>1-back	n.s.	n.s.	n.s.	n.s.
Parietal	0-back>1-back=2-back	0-back>1-back	n.s.	n.s.	n.s.	n.s.
Occipital	0-back>2-back	0-back>1-back	n.s.	AD<NEC	AD<NEC	n.s.
Beta						
Frontal	n.s.	n.s.	0-back>1-back	n.s.	AD<MCI=NEC	n.s.
Central	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
Parietal	n.s.	n.s.	1-back<2-back	AD<NEC	AD<NEC	n.s.
Occipital	n.s.	n.s.	1-back<0-back=2-back	AD<NEC	AD<MCI=NEC	n.s.
Gamma						
Frontal	n.s.	n.s.	0-back>1-back	n.s.	AD<MCI	n.s.
Central	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
Parietal	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
Occipital	n.s.	n.s.	1-back<2-back	n.s.	n.s.	n.s.

Note. NEC = normal elderly controls; MCI = mild cognitive impairment; AD = Alzheimer's disease. Effects reported as significant are $p < .05$.

Table 4.3.

EEG Coherence: Effect of Working Memory Load During the N-back Task for Cross-Hemisphere Homologous Pairs

		Type of effect	*F*	df	*p*	η^2_p	ε	Post-hoc[a]
Delta	NEC	n.s.						
	MCI	WM load x pair	2.78	4, 80	.046	.12	.785	0-back<1-back=2-back (F3-F4)
	AD	WM load x pair	4.00	4, 60	.006	.21	--	0-back=1-back<2-back (O1-O2)
Theta	NEC	WM load	5.65	2, 50	.009	.18	.861	0-back<1-back=2-back
	MCI	n.s.						
	AD	n.s.						
Alpha	NEC	WM load x pair	3.90	4, 100	.011	.14	.773	0-back=2-back>1-back (F3-F4)
	MCI	n.s.						
	AD	n.s.						
Beta	NEC	n.s.						
	MCI	n.s.						
	AD	n.s.						
Gamma	NEC	n.s.						
	MCI	n.s.						
	AD	WM load x pair	4.15	4, 60	.005	.22	--	0-back<2-back (F3-F4)

Note. NEC = normal elderly controls; MCI = mild cognitive impairment; AD = Alzheimer's disease. [a]$p < .05$.

Table 4.4.

EEG Coherence: Group Differences During the N-back Task for Cross-Hemisphere Homologous Pairs

		Type of effect	*F*	df	*p*	η^2_p	ε	Post-hoc[a]
Delta	0-back	Group	10.30	2, 60	<.001	.26	--	AD<MCI=NEC
	1-back	Group	11.90	2, 60	<001	.28	--	AD<MCI=NEC
	2-back	Group (trend)	3.02	2, 60	.056	.09	--	AD<MCI; Trend for AD<NEC[b]
	1b - 0b	n.s.						
	2b - 1b	Group x pair	3.53	4, 120	.011	.11	.924	AD>MCI=NEC (O1-O2)
Theta	0-back	Group	17.29	2, 60	<.001	.37	--	AD<MCI=NEC
	1-back	Group	18.47	2, 60	<.001	.38	--	AD<MCI=NEC
	2-back	Group	12.42	2, 60	<.001	.29	--	AD<MCI=NEC
	1b - 0b	n.s.						
	2b - 1b	n.s.						
Alpha	0-back	Group	7.31	2, 60	.001	.20	--	AD<MCI=NEC
	1-back	Group	7.75	2, 60	.001	.21	--	AD<MCI=NEC
	2-back	Group	10.45	2, 60	<.001	.26	--	AD<MCI=NEC
	1b - 0b	Group x pair	2.53	4, 120	.044	.08	--	MCI>NEC (F3-F4)
	2b - 1b	n.s.						
Beta	0-back	n.s.						
	1-back	n.s.						
	2-back	n.s.						
	1b - 0b	Group	3.68	2, 60	.031	.11	--	AD<MCI; Trend for AD<NEC[c]
	2b - 1b	Group x pair	2.89	4, 120	.028	.09	.965	MCI<NEC=AD (F3-F4)
Gamma	0-back	n.s.						
	1-back	n.s.						
	2-back	n.s.						
	1b - 0b	Group x pair	2.54	4, 120	.048	.08	.932	AD<MCI=NEC (O1-O2)
	2b - 1b	n.s.						

Note. NEC = normal elderly controls; MCI = mild cognitive impairment; AD = Alzheimer's disease; 0b = 0-back; 1b = 1-back; 2b = 2-back. [a]$p < .05$. [b]$p = .063$. [c]$p = .082$.

Table 4.5.
EEG Coherence: Effect of Working Memory Load During the N-back Task for Intrahemispheric Pairs

		F	df	*p*	η^2_p	ε	Post-hoc[a]
F3-P3							
Delta	NEC	4.47	2, 50	.016	.15	--	0-back=1-back>2-back
	MCI	0.39	2, 40	.680	.02	--	
	AD	1.60	2, 30	.218	.10	--	
Theta	NEC	7.75	2, 50	.001	.24	--	0-back=1-back<2-back
	MCI	8.13	2, 40	.001	.29	--	0-back=1-back<2-back
	AD	0.12	2, 30	.889	.01	--	
Alpha	NEC	3.75	2, 50	.030	.13	--	0-back<2-back
	MCI	8.84	2, 40	.001	.31	--	0-back=1-back<2-back
	AD	0.23	2, 30	.795	.02	--	
Beta	NEC	3.20	2, 50	.049	.11	--	0-back<2-back
	MCI	12.29	2, 40	<.001	.38	--	0-back<1-back=2-back
	AD	0.44	2, 30	.591	.03	.744	
Gamma	NEC	2.01	2, 50	.144	.07	--	
	MCI	7.91	2, 40	.003	.28	.824	0-back<1-back
	AD	0.57	2, 30	.571	.04	--	
F3-01							
Delta	NEC	0.91	2, 50	.410	.04	--	
	MCI	1.73	2, 40	.198	.08	.769	0-back<1-back
	AD	2.43	2, 30	.015	.14	--	
Theta	NEC	3.17	2, 50	.061	.11	.830	0-back<2-back
	MCI	7.82	2, 40	.001	.28	--	0-back=1-back<2-back
	AD	2.78	2, 30	.078	.16	--	1-back<2-back
Alpha	NEC	7.01	2, 50	.005	.22	.761	0-back=1-back<2-back
	MCI	8.84	2, 40	.001	.31	--	0-back=1-back<2-back
	AD	2.84	2, 30	.074	.16	--	1-back<2-back
Beta	NEC	9.94	2, 50	<.001	.28	--	0-back=1-back<2-back
	MCI	6.06	2, 40	.005	.23	--	0-back<2-back
	AD	6.08	2, 30	.006	.29		0-back<2-back
Gamma	NEC	11.94	2, 50	<.001	.32	--	0-back=1-back<2-back
	MCI	5.12	2, 40	.013	.20	--	0-back<1-back=2-back
	AD	3.38	2, 30	.047	.18	--	0-back<1-back=2back

Note. NEC = normal elderly controls; MCI = mild cognitive impairment; AD = Alzheimer's disease. [a]$p < .05$.

Table 4.6.
EEG Coherence: Group Differences During the N-back Task for the Fronto-parietal Electrode Pair

		F	*p*	η^2_p	Post-hoc[a]
Delta	0-back	1.22	.302	.04	
	1-back	2.45	.095	.08	AD<NEC
	2-back	2.66	.078	.08	AD<MCI
	1b - 0b	0.85	.433	.03	
	2b - 1b	2.03	.140	.06	
Theta	0-back	0.22	.802	.01	
	1-back	0.61	.547	.02	
	2-back	2.50	.090	.08	AD<MCI
	1b - 0b	0.84	.437	.03	
	2b - 1b	3.07	.054	.09	AD<NEC
Alpha	0-back	0.32	.730	.01	
	1-back	1.47	.239	.05	
	2-back	3.37	.041	.10	AD<MCI
	1b - 0b	2.00	.144	.06	
	2b - 1b	2.25	.114	.07	
Beta	0-back	0.48	.619	.02	
	1-back	1.70	.191	.05	
	2-back	0.80	.456	.03	
	1b - 0b	6.43	.003	.18	AD=NEC<MCI
	2b - 1b	1.45	.243	.05	
Gamma	0-back	0.41	.668	.01	
	1-back	0.00	.997	.00	
	2-back	0.45	.641	.02	
	1b - 0b	0.87	.426	.03	
	2b - 1b	0.15	.861	.01	

Note. NEC = normal elderly controls; MCI = mild cognitive impairment; AD = Alzheimer's disease. df = 2, 60 in all cases. [a]$p < .05$.

Table 4.7.

Intercorrelations Between Neuroimaging Measures and Correlations Between Neuroimaging and N-back Performance

	Normal Elderly Controls			Mild Cognitive Impairment			Alzhiemer's Disease		
Neuroimaging Measures	**Variables**	***r***	***p***	**Variables**	***r***	***p***	**Variables**	***r***	***p***
1-back minus 0-back Coherence & Cortical Thickness	None			Theta F3-F4 & Middle Frontal Gyrus	.517	.033	Theta F3-F4 & Middle Frontal Gyrus	.871	.011
				Alpha F3-F4 & Superior Parietal Lobule	.496	.043	Beta F3-F4 & Superior Frontal Gyrus	-.763	.046
							Gamma F3-F4 & Anterior Cingulate Cortex	.812	.027
				Theta P3-P4 & Superior Frontal Gyrus	-.554	.021	Beta P3-P4 & Superior Parietal Lobule	.829	.021
				Theta P3-P4 & Superior Parietal Lobule	**-.657**	**.004**			
				Alpha F3-P3 & Anterior Cingulate Cortex	**.613**	**.009**			
1-back minus 0-back Coherence & PiB Retention	Gamma F3-F4 & Anterior Cingulate Cortex	.760	.011				Alpha F3-F4 & Superior Frontal Gyrus	-.784	.037
	Gamma F3-F4 & Superior Parietal Lobule	**.819**	**.004**						
				Gamma P3-P4 & Superior Frontal Gyrus	-.628	.022			
				Gamma P3-P4 & Middle Frontal Gyrus	-.579	.038			
				Gamma P3-P4 & Anterior Cingulate Cortex	-.564	.045			
				Gamma P3-P4 & Superior Parietal Lobule	-.566	.044			
							Delta F3-P3 & Middle Frontal Gyrus	-.761	.047

Neuroimaging & N-back Behaviour	**Variables**	***r***	***p***	**Variables**	***r***	***p***	**Variables**	***r***	***p***
1-back minus 0-back Coherence & 1-back Behaviour	None						Delta F3-F4 & 1-back RT	.516	.041
							Delta F3-F4 & 1-back Accuracy	**-.708**	**.002**
							Beta F3-F4 & 1-back RT	.582	.018
							Gamma F3-F4 & 1-back Accuracy	**-.652**	**.006**
				Alpha P3-P4 & 1-back RT	-.435	.049			
				Beta P3-P4 & 1-back Accuracy	-.514	.017			
							Alpha F3-P3 & 1-back Accuracy	**-.672**	**.004**
							Gamma F3-P3 & 1-back RT	**.671**	**.004**
Cortical Thickness & 1-back Behaviour	None			None			None		
PiB Retention & 1-back Behaviour	None			Superior Parietal Lobule & 1-back Accuracy	-.681	.010	None		

Note. Bolded entries indicate $p < .01$.

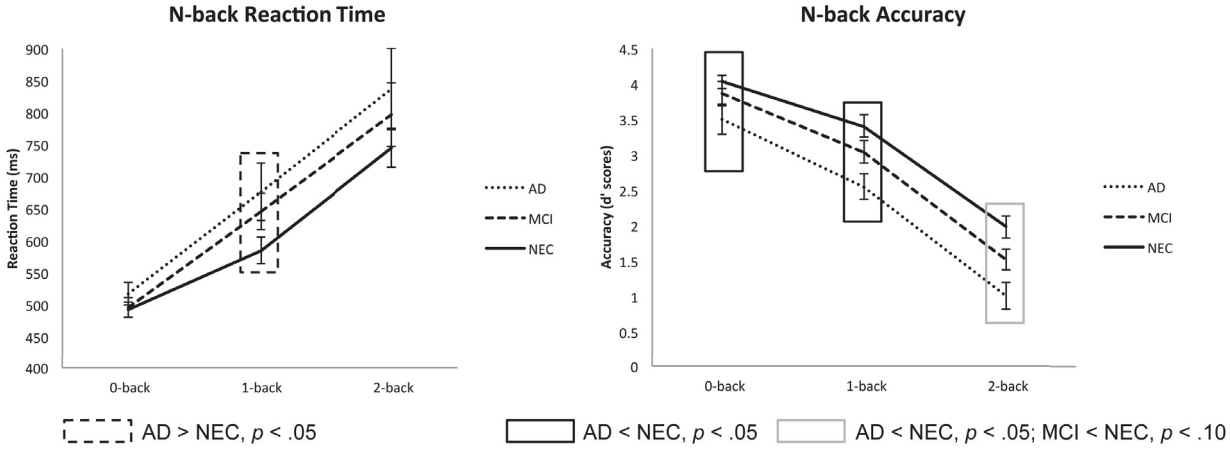

Figure 4.1. Reaction time and accuracy for the N-back task for patients with Alzheimer's disease (AD), patients with mild cognitive impairment (MCI), and normal elderly controls (NECs). Error bars represent one standard error of the mean.

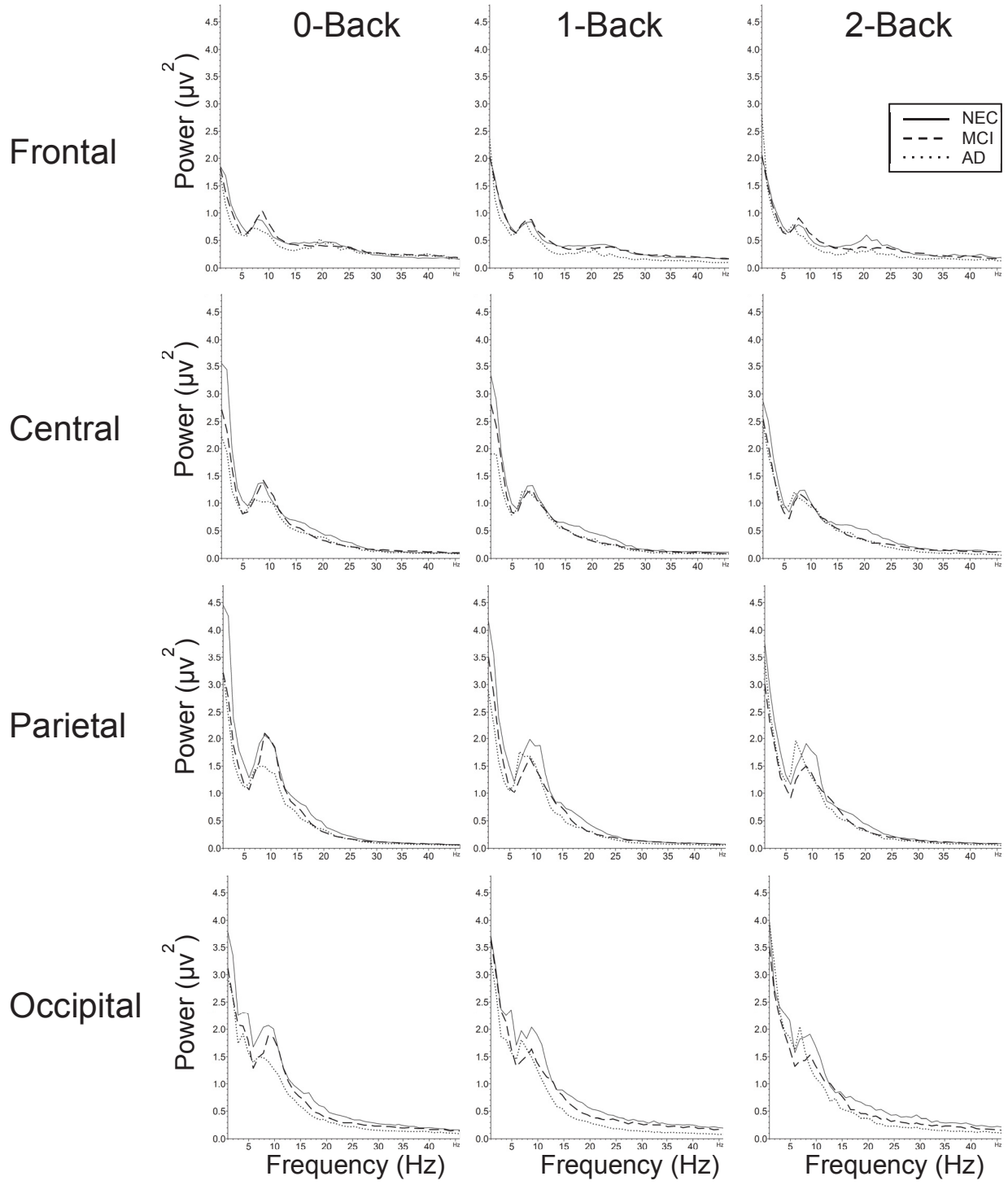

Figure 4.2. Mean power during the N-back task (0-back, 1-back, 2-back) at frontal (F3, Fz, F4), central (C3, Cz, C4), parietal (P3, Pz, P4), and occipital (O1, O2) electrode sites for normal elderly controls (NEC), patients with mild cognitive impairment (MCI), and patients with Alzheimer's disease (AD).

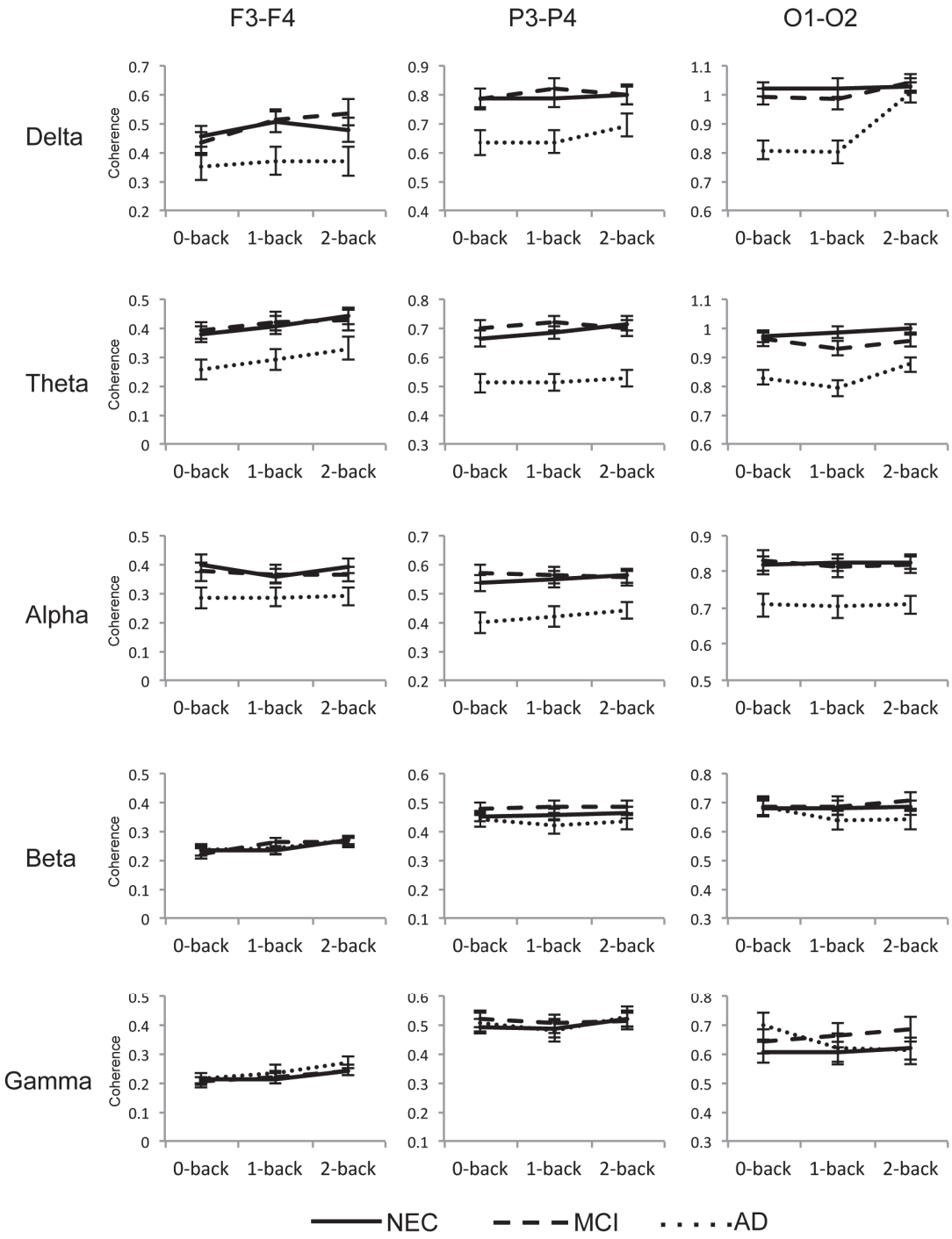

Figure 4.3. EEG coherence values for cross-hemisphere electrode pairs for Normal Elderly Controls (NECs), patients with mild cognitive impairment (MCI), and patients with Alzheimer's disease (AD) during the N-back task. Data are square root and Fisher's Z transformed. Error bars represent the standard error of the mean. Note that the scale on the y-axis varies by electrode pair, though the range remains constant.

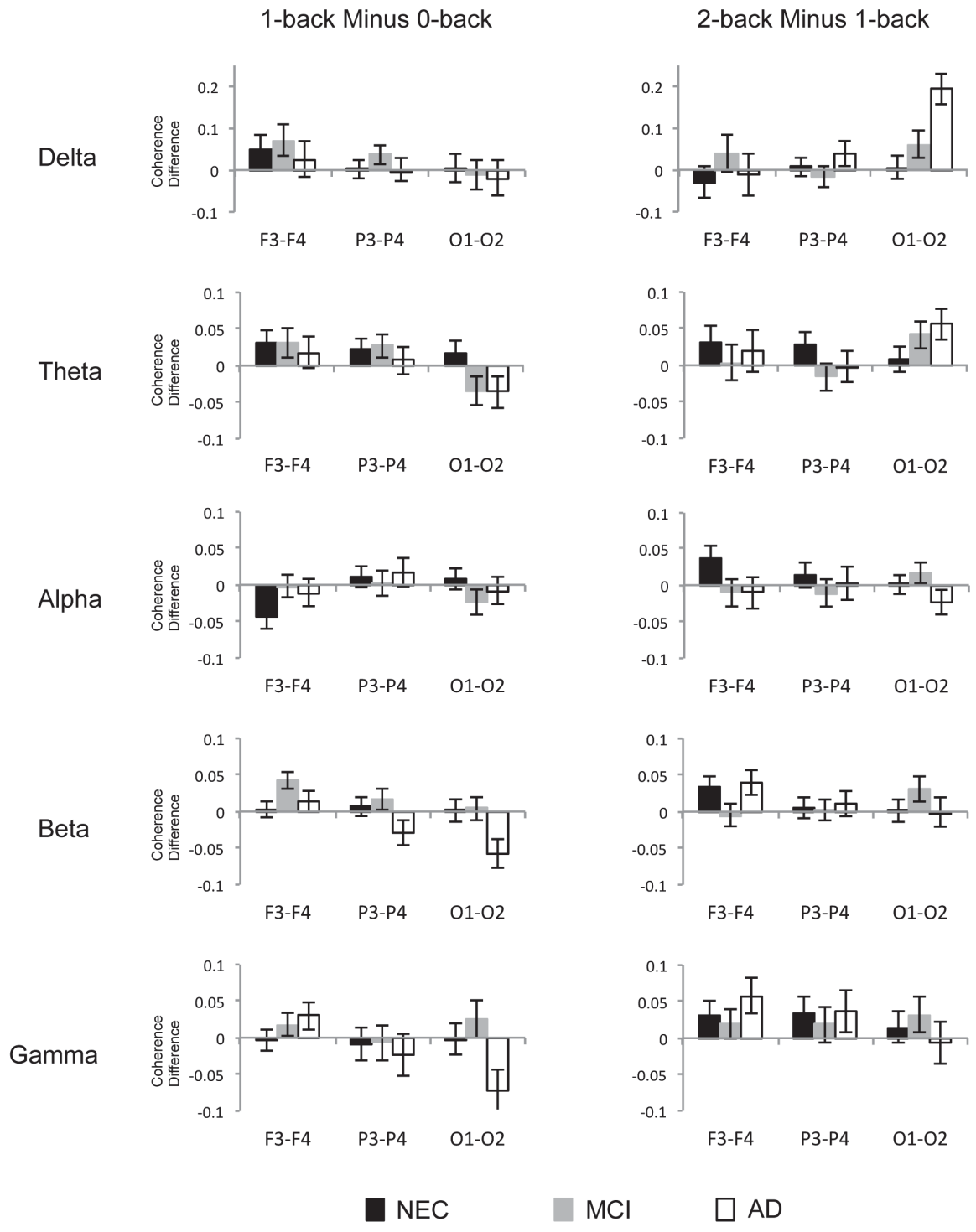

Figure 4.4. EEG coherence difference scores for the N-back task for cross-hemisphere electrode pairs for Normal Elderly Controls (NECs), patients with mild cognitive impairment (MCI), and patients with Alzheimer's disease (AD). Data are square root and Fisher's Z transformed. Error bars represent the standard error of the mean.

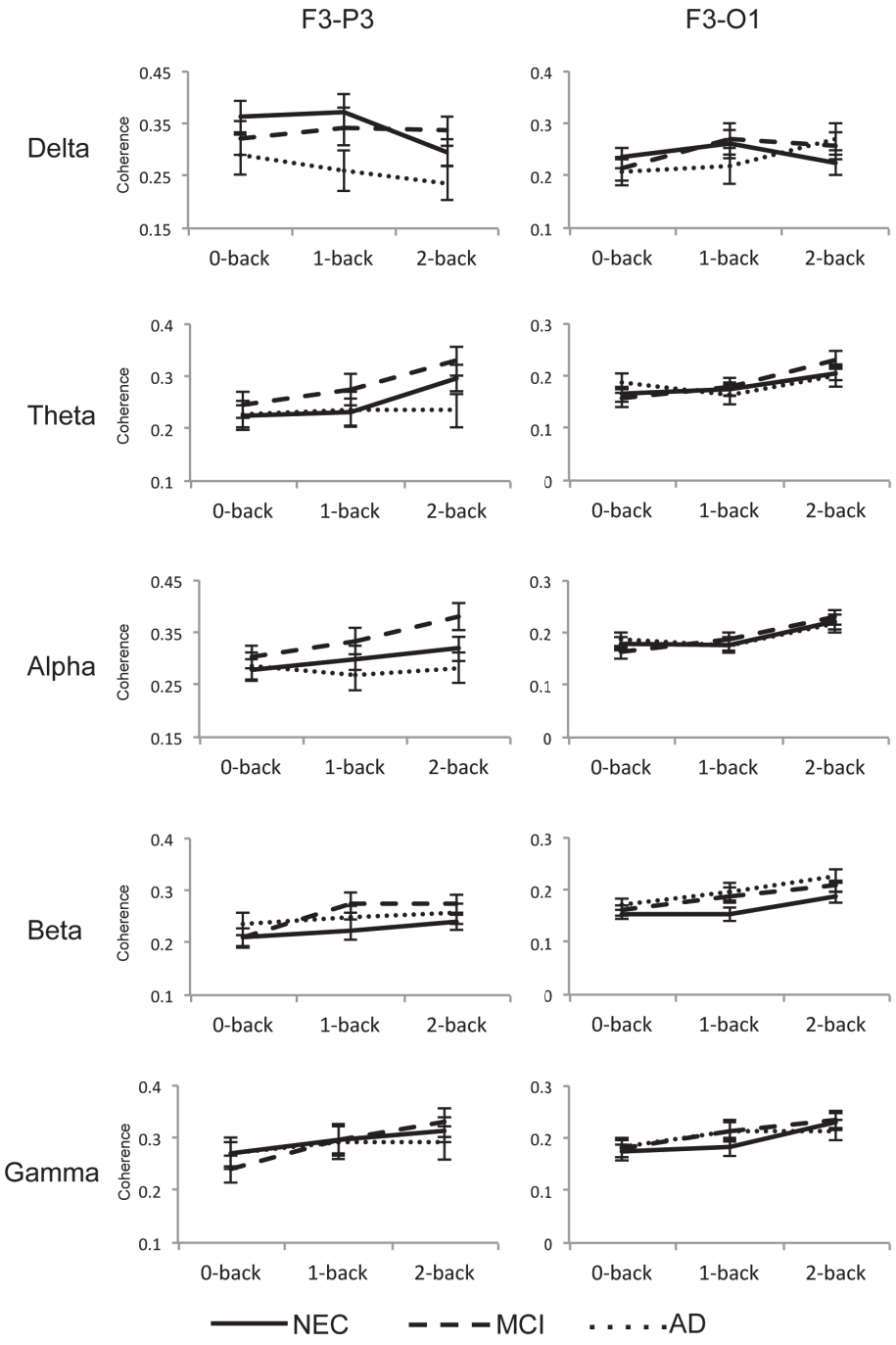

Figure 4.5. EEG coherence values for intrahemispheric electrode pairs for Normal Elderly Controls (NECs), patients with mild cognitive impairment (MCI), and patients with Alzheimer's disease (AD) during the N-back task. Data are square root and Fisher's Z transformed. Error bars represent the standard error of the mean. Note that the scale on the y-axis varies by electrode pair, though the range remains constant.

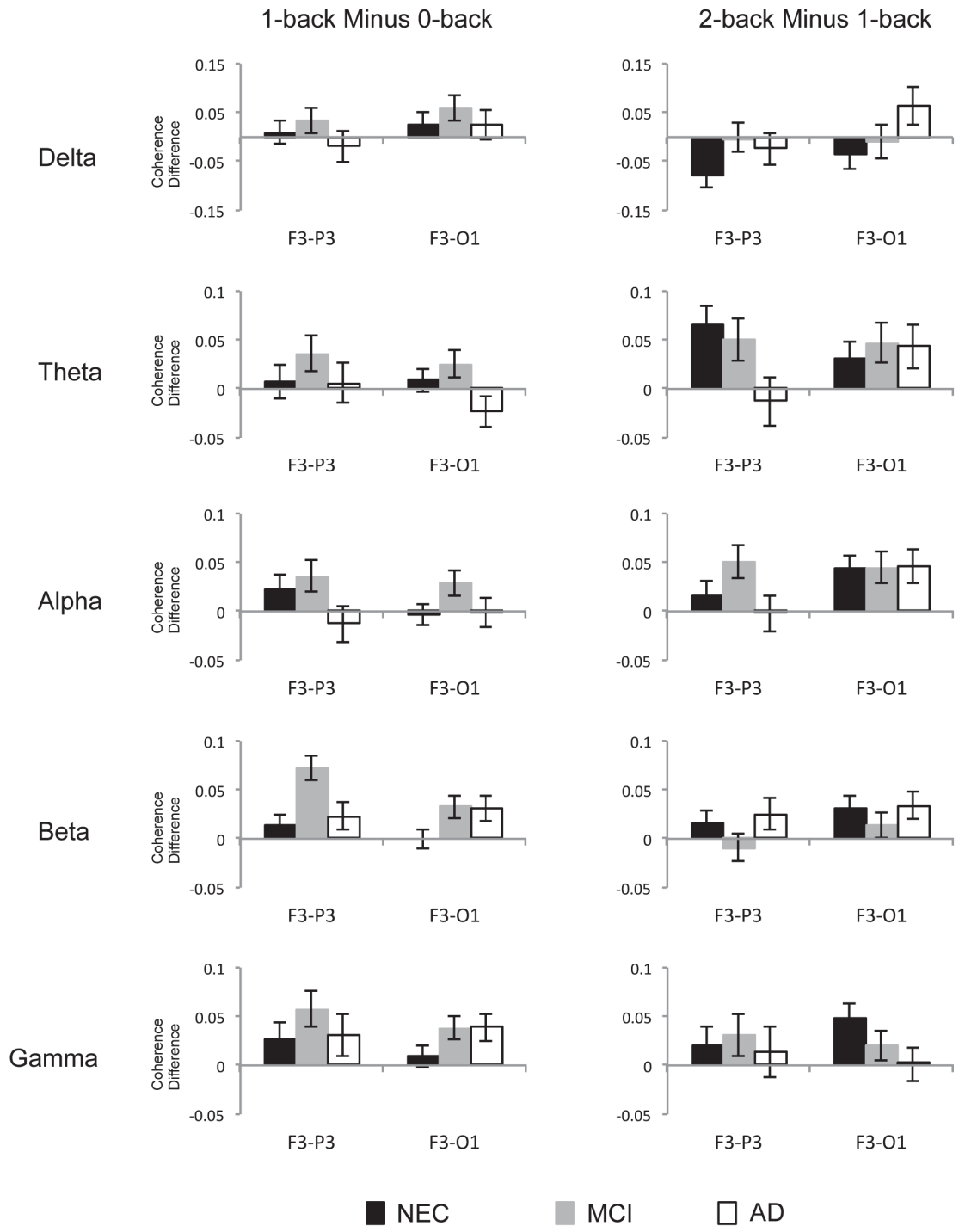

Figure 4.6. EEG coherence difference scores for intrahemispheric electrode pairs during the N-back task for Normal Elderly Controls (NECs), patients with mild cognitive impairment (MCI), and patients with Alzheimer's disease (AD). Data are square root and Fisher's Z transformed. Error bars represent the standard error of the mean.

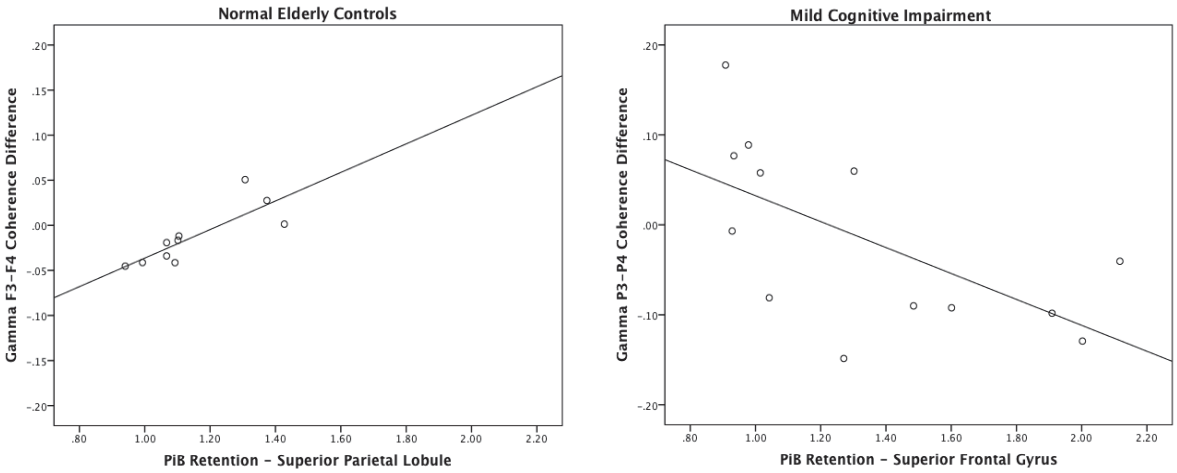

Figure 4.7. Sample scatterplots for EEG coherence difference (1-back minus 0-back) and PiB retention in normal elderly controls (gamma F3-F4) and mild cognitive impairment (gamma P3-P4).

CHAPTER 5: GENERAL DISCUSSION

Alzheimer's disease is increasingly viewed as a disconnection syndrome involving alterations in the functional connectivity between brain regions (Bokde et al., 2009; De Lacoste & White, 1993; Delbeuck et al., 2003). This is an interesting proposal given the fact that certain cognitive deficits seen early in the course of the disease cannot easily be explained by neuronal atrophy. In particular, executive dysfunction is present in the prodromal phase of AD (e.g., Albert et al., 2007; Johns et al., 2012; Perri et al., 2007), before significant atrophy is seen in the frontal lobes (Whitwell, Przybelski, et al., 2007b). Thus, deficits in executive functioning may be related to changes in functional brain connectivity.

The overarching goal of this dissertation was to explore functional connectivity in AD and MCI using EEG coherence, and in particular, how coherence is affected during the performance of executive functioning tasks. Additionally, the relationship between EEG coherence and neuropathology (cortical thickness and amyloid deposition) was explored, along with the relationships between neuroimaging and cognitive measures. Specifically, the three manuscripts presented in this paper aimed to address EEG coherence measured at rest (manuscript 1), and EEG coherence measured during the performance of two types of executive functioning tasks, namely inhibitory control (Go/No-go task, manuscript 2) and working memory (N-back task, manuscript 3). We obtained multiple cognitive (neuropsychological test performance, experimental task performance) and neuroimaging measures (EEG coherence, cortical thickness, PiB retention), allowing us to explore multiple aspects of neuropathology and cognitive functioning within the same group of participants. This general discussion begins with an integrated summary of the results of the three studies, followed by a discussion of the theoretical and clinical implications of the results, and the strengths and limitations of these studies. Finally, directions for future research will be explored.

5.1 Cognitive Functioning in AD & MCI

Results from neuropsychological testing confirmed the presence of a prominent deficit in episodic memory in both AD patients and MCI patients. The two groups also showed deficits in a number of other cognitive domains, including verbal abstract reasoning, processing speed, semantic verbal fluency, and semantic inhibition. AD patients additionally showed deficits in confrontational naming, short-term memory span, phonemic verbal fluency, working memory, and prepotent response inhibition. Though the differences did not reach statistical significance,

MCI patients also demonstrated trends towards deficits in short-term memory span and working memory. Thus, neuropsychological testing confirmed executive dysfunction in both AD and MCI patients, including difficulties with inhibition and working memory. On experimental tasks, both AD and MCI patients had slower reaction times but preserved accuracy on the Go/No-go task, and on the N-back task, only AD patients had slower reaction times for the 1-back condition, and lower accuracy for all working memory loads. There was a trend towards lower accuracy for the 2-back condition in MCI patients. Overall, our results suggest that AD patients exhibit deficits on both measures of inhibition and measures of working memory, whereas in MCI patients, tasks of inhibitory control are more sensitive to detecting deficits, though there is a consistent tendency towards lower performance on working memory tasks. This is consistent with previous findings that deficits in inhibitory control are particularly prominent in MCI patients (Johns et al., 2012).

5.2 Neuropathology

The pattern of cortical thickness and PiB retention in AD and MCI patients in the present study was consistent with previous studies (Berti et al., 2010; Masdeu et al., 2012; Román & Pascual, 2012). Cortical thickness was reduced in the parahippocampal gyrus in both AD patients and MCI patients, and in the anterior cingulate cortex in AD patients. We also found elevated PiB retention in the superior frontal gyrus, middle frontal gyrus, anterior cingulate cortex, and superior parietal lobule in AD patients. In MCI patients, PiB retention was elevated in the superior frontal gyrus, and there was a tendency towards higher PiB retention in the middle frontal gyrus and anterior cingulate cortex.

5.3 EEG Coherence

The overall pattern of our results indicated that AD patients show reduced functional connectivity within a fronto-parietal network while at rest and additional reductions in connectivity during the performance of tasks of executive functioning. In contrast, MCI patients show preserved resting functional connectivity, but altered connectivity during the performance of executive tasks. Specifically, AD patients showed reduced cross-hemisphere parietal coherence in the delta and theta bands while at rest and reduced parietal theta coherence during sustained attention trials of the Go/No-go task. Additional reductions were seen during tasks and conditions requiring executive functions. Frontal theta coherence was additionally reduced during inhibition trials on the Go/No-go task, and frontal and occipital delta, theta, and alpha

coherence was additionally reduced during the N-back task. Furthermore, AD patients showed less of an increase in cross-hemisphere beta coherence from 0-back to 1-back and less of an increase in fronto-parietal theta coherence from 1-back to 2-back. Thus, AD patients demonstrate reductions in cross-hemisphere, but not intrahemispheric connectivity, which are more widespread during the performance of executive tasks, encompassing frontal regions. Some previous studies have reported more widespread decreases in synchronization in AD patients, including for fronto-parietal pairs (e.g., C. Babiloni, Ferri, et al., 2004b; 2006b). However, these studies used a different method of calculating synchronization (synchronization likelihood), therefore it is difficult to directly compare the results.

While MCI patients showed preserved resting coherence, they exhibited higher fronto-parietal alpha coherence for inhibition trials in the Go/No-go task. In addition, MCI patients showed a greater coherence difference (No-go trials minus Go trials) in fronto-parietal alpha, and a smaller difference in frontal theta coherence. On the N-back task, though there were no differences between MCI patients and controls at any of the working memory loads, some interesting differences emerged for the modulation of coherence with working memory load. In MCI patients, coherence tended to increase at a lower working memory load than for normal controls. In addition, MCI patients showed a greater increase in frontal alpha and intrahemispheric beta coherence from 0-back to 1-back and less of an increase in frontal beta coherence from 1-back to 2-back. Therefore, in MCI patients, alterations in functional connectivity may be present only during the performance of a cognitive task. This is consistent with the results of a previous study that found no difference in EEG coherence between MCI patients and controls during a resting condition, but a widespread increase in coherence during the performance of a working memory task (Jiang et al., 2008). This suggests that examining changes in how EEG coherence is affected by task difficulty may offer some important insights into alterations in functional connectivity in MCI that may not be observable during resting conditions.

MCI patients who converted to dementia over a period of approximately three years showed higher resting fronto-parietal gamma coherence. In addition, though the data were not presented in the manuscripts, we examined group differences on EEG coherence during the performance of cognitive tasks between MCI patients who remained stable and those who converted to dementia. We found very few differences between groups on measures of EEG

coherence during task performance. On the Go/No-go task, there was only a trend towards a smaller increase in cross-hemisphere alpha coherence with inhibitory demands in MCI patients who converted to dementia, $F(1, 14) = 3.16$, $p = .097$, $\eta^2_p = .185$. On the N-back task, while stable MCI patients showed an increase in cross-hemisphere frontal alpha coherence from 1-back to 2-back, MCI converters showed a decrease in coherence, $F(1, 14) = 7.91$, $p = .014$, $\eta^2_p = .361$. Higher resting fronto-parietal coherence in MCI patient who converted to dementia has been reported in a previous study (Rossini et al., 2006), however, another study reported no difference on baseline coherence in MCI patients who converted to dementia versus those who remained stable (Jelic et al., 2000). Thus, there is some confirmation that higher resting fronto-parietal coherence is present in MCI converters, and the examination of EEG coherence during the performance of tasks of executive functioning provides preliminary evidence for alterations in cross-hemisphere alpha coherence reactivity to task demands in MCI converters. The finding of higher resting fronto-parietal connectivity in MCI converters is somewhat counterintuitive; however, it may represent a short-term compensatory process that is predictive of decline in the long term. Longitudinal studies are required in order to test this hypothesis.

5.4 Relationship Between EEG Coherence and Neuropathology

Though overall, the results from the exploratory correlations were somewhat mixed, some interesting patterns emerged over the three studies. First of all, there were few significant correlations between resting coherence and cortical thickness for any of the groups, but MCI patients showed several significant correlations between Go/No-go coherence and cortical thickness, and both AD and MCI patients showed several correlations between N-back coherence and cortical thickness. Thus, overall, normal controls did not show a reliable relationship between EEG coherence and cortical thickness. For MCI patients, lower cortical thickness was associated with less of an increase in cross-hemisphere frontal and fronto-parietal coherence with working memory load on the N-back task, but a larger increase in cross-hemisphere parietal coherence with working memory load. In addition, lower cortical thickness was associated with a larger increase in cross-hemisphere frontal and parietal coherence in response to inhibitory demands on the Go/No-go task. These findings of increased coherence in response to task demands in individuals with lower cortical thickness is counterintuitive and could reflect a compensatory mechanism (discussed in more detail below). For AD patients, lower cortical thickness was associated with smaller increase in cross-hemisphere parietal

coherence for the Go/No-go task and a smaller increase in cross-hemisphere frontal and parietal coherence for the N-back task. This finding is in the expected direction and suggests that neurodegeneration has a negative impact on interhemispheric functional connectivity in AD patients.

With respect to PiB retention, normal controls and MCI patients showed relationships between PiB retention and coherence at rest and during the performance of both executive function tasks. In contrast, AD patients showed fewer significant relationships between PiB retention and EEG coherence, and only for coherence during task performance. In normal controls, higher PiB retention was associated with (1) lower cross-hemisphere coherence at rest and during the Go/No-go task, and (2) higher fronto-parietal coherence at rest and higher cross-hemisphere frontal coherence during the N-back task. In MCI patients, higher PiB retention was associated with (1) lower frontal and fronto-parietal coherence at rest, (2) higher cross-hemisphere parietal coherence during the Go/No-go task, and (3) lower cross-hemisphere parietal coherence during the N-back task. In AD patients, higher PiB retention was associated with a smaller increase in frontal and fronto-parietal coherence during the Go/No-go task and the N-back task. Thus, in AD patients, though there are few reliable correlations between EEG coherence and PiB retention, they are consistently in the negative direction. In contrast, for normal controls and MCI patients, coherence is sometimes negatively related with PiB retention, and sometimes positively related with PiB retention. The possible implications of these findings are discussed below.

5.5 Relationship Between Neuroimaging Measures and Cognition

Performance on the experimental tasks was not reliably associated with EEG coherence during task performance in normal controls, and MCI and AD patients showed few significant relationships with neuroimaging measures. On the Go/No-go task, the patient groups showed a pattern in which a greater increase in parietal and fronto-parietal coherence was associated with faster response times, but lower accuracy. On the N-back task, a greater increase in cross-hemisphere parietal coherence was also associated with faster response times and lower accuracy in MCI patients; however, in AD patients, a greater increase in frontal and fronto-parietal coherence was associated with longer response times and lower accuracy. Thus, overall, the relationship between EEG coherence and performance on the experimental tasks is somewhat inconsistent across the three groups.

However, there were a greater number of significant correlations between neuroimaging and neuropsychological test performance. Refer to Table 5.1 for a summary of the relationships between cortical thickness, PiB retention, EEG coherence, and performance on selected neuropsychological tests (MoCA, CVLT, Trail Making Test, LNS, Stroop test, Hayling test), including relationships with Go/No-go coherence and N-back coherence not presented in the manuscripts of this thesis. Note that for ease of interpretation, a positive relationship between the neuroimaging measures and better performance on neuropsychological tests is indicated in bold. As can be seen from the table, though there are few significant correlations for cortical thickness and PiB retention with neuropsychological tests, the pattern is generally consistent. In NECs and AD patients, greater cortical thickness is associated with better test performance, whereas in MCI patients, greater thickness is associated with poorer test performance. For PiB, greater retention is associated with poorer test performance in the three groups. For EEG coherence, the weight of the evidence points towards a negative relationship with test performance in normal controls (higher coherence is associated with poorer performance on neuropsychological tests). One possible interpretation of this relationship is that it is reflective of inefficient neural recruitment on the part of older adults with lower cognitive function. In MCI patients, the pattern is mixed, and in AD patients, there appears to be a positive relationship with test performance for resting coherence and coherence during the Go/No-go task, and a negative relationship with test performance for coherence increase from 0-back to 1-back during the N-back task.

5.6 Theoretical Implications

5.6.1 Functional disconnection in AD patients. Overall, the results from the three studies support the disconnection hypothesis of AD, which proposes that cognitive deficits may be due to the failure of interaction between regions of a neural network, rather than isolated changes in specific areas (Bokde et al., 2009). It has been demonstrated that the neuropathological hallmarks of AD (neurofibrillary tangles and amyloid plaques) affect predominantly cortico-cortical tracts that connect brain areas both within and between hemispheres (for a review, see Delbeuck et al., 2003). In particular, neurofibrillary tangles predominate in brain areas that give rise to cortico-cortical tracts, whereas amyloid plaques predominate at the ends of these tracts (De Lacoste & White, 1993; Delbeuck et al., 2003). Thus, the neuropathology of AD may primarily involve these cortico-cortical connections, resulting in

disconnection between cortical areas. Previous studies of EEG synchronization in AD patients have found decreased synchronization both within and between hemispheres (e.g., Adler et al., 2003; Kai et al., 2005; Knott et al., 2000; Sankari et al., 2012), including between frontal and parietal regions (C. Babiloni, Ferri, et al., 2004b; 2006b; Başar et al., 2010; Güntekin et al., 2008). The results presented here confirm functional disconnection between hemispheres in AD patients; however, we did not find evidence for reduced fronto-parietal connectivity.

5.6.2 Neural compensation in MCI patients. A different pattern emerged for MCI patients. The results did not support the presence of functional disconnection within a network of frontal and parietal regions, as has been reported in previous studies (e.g., C. Babiloni, Ferri, et al., 2006b; Moretti et al., 2008; Tóth et al., 2014). However, studies of EEG synchronization in MCI patients have been mixed, with some studies finding no differences between MCI patients and controls (e.g., Stam et al., 2003) and others reporting an increase in coherence in MCI patients (e.g., Bajo et al., 2010; Jiang et al., 2008; Moretti et al., 2008; Pijnenburg et al., 2004). The results of the studies presented in this dissertation do, however, support the presence of altered functional connectivity in MCI patients during the performance of a cognitive task. In two cases, there was less of a difference in MCI patients versus controls between trial types or conditions: (1) frontal theta for No-go minus Go, and (2) frontal beta for 2-back minus 1-back. In one case, increased coherence was observed for a specific trial type, namely increased fronto-parietal alpha coherence during No-go trials. Finally, a greater difference between trial types or conditions was observed in three cases: (1) fronto-parietal alpha for No-go minus Go, (2) frontal alpha for 1-back minus 0-back, and (3) fronto-parietal beta for 1-back minus 0-back.

Decreased brain activation, lower coherence, and by extension less of a difference in coherence between trial type or condition is generally agreed to be reflective of cognitive decline (C. Babiloni et al., 2011; Reuter-Lorenz & Cappell, 2008; Saliasi, Geerligs, Lorist, & Maurits, 2014). However, increases in activation, more widespread activation, or increases in synchronization may be interpreted in one of two ways. These increases may represent compensatory processes, or on the other hand, may represent inefficient recruitment of neural resources (Reuter-Lorenz & Cappell, 2008; Reuter-Lorenz & Lustig, 2005; Saliasi et al., 2014). A theory of neural compensation, the compensation-related utilization of neural circuits hypothesis, or CRUNCH, was proposed in order to account for the common finding of overactivation in the brains of older adults in comparison to younger adults (Reuter-Lorenz &

Cappell, 2008). This hypothesis posits that older adults require more neural resources to maintain the same level of performance as younger adults. Thus, at lower levels of task demand, older adults recruit additional neural resources in order to maintain cognitive performance comparable to that of younger adults, but that at higher levels of task demand, older adults reach a capacity limit for neural resources, resulting in underactivation relative to younger adults and a decline in performance. In contrast, dedifferentiation refers to the breakdown of the selectivity and specificity of neural resources, thus resulting in more widespread, but inefficient neural activation (Reuter-Lorenz & Cappell, 2008).

The results from the sample of MCI patients presented in this dissertation are most consistent with CRUNCH. In a similar manner to what has been reported in normal aging, MCI patients exhibited increased coherence (or a trend in that direction) and preserved performance at lower levels of task demand relative to controls (higher frontal coherence for Go trials and a greater increase in frontal and fronto-parietal coherence from 0-back to 1-back). In contrast, there was less of an increase in coherence with increasing task demand (a smaller increase in frontal coherence for No-go trials vs. Go trials, and from 1-back to 2-back). In the case of the N-back task, the smaller increase in coherence at the highest working memory load coincided with a drop in accuracy. Thus, these results support a similar neural compensation process in MCI patients relative to healthy older adults as has previously been reported in healthy older adults relative to younger adults.

In MCI patients, greater neuropathology was also sometimes associated with a larger increase in coherence with increased executive demand. This could be interpreted as a compensatory process for increasing pathological burden at certain levels of task performance. Specifically, lower cortical thickness and higher PiB retention were associated with a greater increase in cross-hemisphere coherence for No-go trials in comparison to Go trials for frontal (cortical thickness) and parietal (cortical thickness and PiB retention) electrode pairs. However, this pattern was not observed for resting coherence or N-back coherence, where higher neuropathology was most often associated with lower coherence. Therefore, it is possible that MCI patients with higher pathological burden are able to recruit compensatory processes in response to the task demands of the Go/No-go task, but not for the N-back task.

5.6.3 Neural compensation in normal controls. In normal controls, higher PiB retention was associated with higher resting fronto-parietal coherence in the theta and gamma

bands, but with lower cross-hemisphere frontal and parietal coherence. Thus, with increasing amyloid burden, cross-hemisphere coherence decreases, but fronto-parietal coherence increases. Since normal controls by definition have preserved cognitive function, it may be hypothesized that the increase in fronto-parietal coherence serves to compensate for increasing amyloid burden and maintain good cognition. This is an interesting possibility; however, a more sophisticated experimental design would be required to test this hypothesis. This could be accomplished by examining within-subjects changes in amyloid burden, cognition, and coherence over time.

5.6.4 EEG coherence and cognition. The lack of a strong relationship between neuroimaging measures and cognitive performance has been reported in previous studies using other imaging methods (e.g., PET, fMRI), where increased activation has been observed in MCI and AD patients, but the increased activation does not necessarily lead to improved performance (Lopez, Becker, & Kuller, 2013). Thus, increased activation could be serving to maintain a certain level of cognitive function, albeit still lower than that of controls. Another complimentary possibility is that the lack of a strong association between neuroimaging measures and cognition could be explained in part by the concept of cognitive reserve. Cognitive reserve can be defined as "differences in cognitive processes as a function of lifetime intellectual activities and other environmental factors that explain differential susceptibility to functional impairment in the presence of pathology or other neurological insult" (Barulli & Stern, 2013, p. 502). Previous studies have found that the relationship between AD pathology and cognitive function is moderated by proxy measures of cognitive reserve such as years of education (e.g., Bennett et al., 2003). Thus, different amounts of brain pathology may lead to different cognitive outcomes depending on individual levels of cognitive reserve. Individual differences in brain reserve (premorbid brain capacity, defined by brain volume, number of neurons, number of synapses, etc.) may also play a role. Brain reserve may also be distinguished from neural reserve, which refers to the neural networks that have developed over the course of the lifespan as a result of the same individual experiences that lead to cognitive reserve (Barulli & Stern, 2013). An individual with high neural reserve would likely show more efficient networks, and one may also speculate that individual differences in EEG coherence may be related to neural reserve. Thus, a model accounting for individual differences on several related factors may be required in order to fully understand the relationship between EEG coherence and cognition.

5.7 Clinical Implications

A greater understanding of brain functioning during task performance in AD patients is helpful for providing context and understanding of some of the difficulties that patients face in their daily lives and providing recommendations for patient care. In daily life, tasks that require efficient cross-hemisphere communication are common, and these types of tasks may be particularly difficult for AD patients. For example, dual task situations may be particularly challenging. It would be helpful to educate family members and caregivers as to the underlying neural mechanism that may be the cause of such difficulties and to provide practical suggestions on how to limit dual task requirements, such as giving patients single, discrete tasks to be performed sequentially. This type of intervention may benefit family members and caregivers by improving their understanding of how the neuropathology of AD may affect daily functioning beyond memory impairment, and it may also benefit patients by improving their ability to perform daily tasks if they are presented in this simplified manner.

Finally, training programs designed to improve cross-hemisphere communication may be of benefit to AD patients. Previous studies in healthy older adults have found that cognitive training results in increased cortical thickness, increased structural connectivity, and changes in brain activation patterns (Belleville & Bherer, 2012; Hosseini, Kramer, & Kesler, 2014). Alterations in brain functioning following cognitive training have also been reported in MCI patients (Hosseini et al., 2014). Thus, cognitive training may also improve cross-hemisphere communication in AD patients.

5.8 Strengths and Limitations

A major limitation of the three studies presented here is the relatively small sample size, particularly for the correlational analysis for cortical thickness and PiB retention. The small sample size decreases statistical power to detect differences between groups as well as relationships between variables in the correlational analysis. Smaller sample sizes present a particular difficulty for groups that are highly heterogeneous, such as MCI patients. However, the sample size for correlations with cortical thickness and PiB retention was larger for MCI patients than the other two groups, which may have mitigated this difficulty to a certain degree. The small sample size also limited our ability to use more sophisticated multivariate statistical techniques such as multiple regression. Therefore, we were limited to exploratory bivariate

correlations, which must be interpreted with caution due to the small sample size and the large number of correlations performed.

It is also important to acknowledge that, due to practical constraints, there was a time delay between the measurement of EEG coherence and neuropathology (cortical thickness and PiB). MRI and PiB scans were performed within one year of EEG testing for MCI patients and within two years of EEG testing for normal controls and AD patients. Therefore, the measures of neuropathology may not be entirely representative of the state of the brain at the time of EEG testing, as it is possible that neuropathological changes occurred between the two testing sessions. Obtaining neuropathological measures closer in time to measures of EEG coherence and cognition may have resulted in stronger correlations between these variables.

Some other potential limitations of these studies involve methodological issues related to EEG and the choices made for data selection, averaging, and reduction. Specifically, it is important to acknowledge that we are limited in our ability to determine the sources in the brain that generate the EEG signal at the scalp electrodes. The EEG signal is known to be affected by multiple generators, whose electrical signals are volume conducted through brain tissue and spatially smeared at the scalp (Luck, 2005). Therefore, we cannot be exact about which specific brain regions give rise to the signal recorded at a particular electrode site. One generator can contribute to shared activity recorded at two different electrode sites, potentially resulting in artificially elevated coherence values between those sites. The use of a common reference in the EEG recording may also contribute to shared activity recorded at different sites (Nunez et al., 1997). This has several important implications for the studies presented in this dissertation. Most notably, we cannot be certain that we are specifically examining activity within a fronto-parietal network when comparing the electrical activity recorded at frontal and parietal sites. Furthermore, we are limited in our ability to interpret the absolute value of coherence for a given electrode pair or to compare coherence between electrode pairs. For this reason, we have focused on comparisons between groups and between experimental conditions for the same electrode pair. These types of comparisons minimize the effects of volume conduction, but must still be interpreted with caution, as it is possible that a third generator contributing to activity at both sites may be active in one experimental condition, but not the other, resulting in artificially elevated coherence in one of the conditions (Roach & Mathalon, 2008). Several techniques have been proposed to reduce the effects of volume conduction on EEG coherence, including the use

of Laplacian transforms or independent components analysis in order to identify activity that is unique to each electrode, as well as source modeling methods and methods of deriving coherence values that are insensitive to signals with zero phase lag between them (as these signals are assumed to reflect activity from the same source) (Nunez et al., 1997; Roach & Mathalon, 2008). Further exploration of the relationship between EEG coherence and executive functioning in MCI and AD patients using these methods and/or using MEG coherence (which has the advantage of higher spatial resolution) will help to more specifically identify the neural sources of the differences observed in EEG coherence.

With regards to our data processing procedures, only correct trials were used in the analysis of EEG coherence for the Go/No-go and N-back tasks. As the underlying neural response for correct trials versus incorrect trials may differ, the two must be considered separately in order to obtain an average that is comprised of similar response types. It could be interesting to explore brain functioning in these groups for correct versus incorrect trials; however, due to the necessity of designing tasks that the patient groups could perform, there was an insufficient number of incorrect trials to reliably calculate coherence on each of the tasks, and therefore the results of these studies can only specifically be applied to instances in which a correct response is produced. Furthermore, we selected epochs of 1024 ms in order to obtain a time window long enough to resolve the lowest frequencies of interest as well as to obtain segments that include the responses for each trial. However, the higher frequency resolution results in a lower temporal resolution, and precludes the analysis of changes in coherence over the course of the trials. This epoch length may also result in placing larger weight on the lower frequency bands. Techniques such as wavelet transformations could be used to examine EEG coherence for smaller time windows within each trial.

In addition, EEG coherence data were averaged for each frequency band, which may have obscured differences that could exist between groups for the lower and higher ranges of a given band. For example, in some studies that have examined smaller frequency windows, differences were restricted to smaller windows within a band, such as lower vs. upper alpha (Hogan et al., 2003; Pijnenburg et al., 2004; e.g., Stam et al., 2005). Finally, in order to limit the number of comparisons, the analyses were restricted to electrode pairs within a fronto-parietal network, and within the left hemisphere for intrahemispheric pairs. These electrode pairs were selected for relevance to executive functioning and the left hemisphere pairs were selected due to

the verbal nature of the tasks; however, there may have been group differences in other electrode pairs that were not examined (e.g., right hemisphere fronto-parietal pairs, local intrahemispheric frontal pairs, fronto-temporal pairs). Furthermore, due to the effects of volume conduction discussed above, it is possible that other electrode pairs may better reflect frontal and parietal sources.

Despite these limitations, the studies presented here have several important strengths. First of all, the samples were well-matched in terms of age and education. In addition, two well-validated measures of executive functioning were used in these studies. Both the Go/No-go and N-back tasks have been used in many neuroimaging studies assessing executive functioning as well as in studies of MCI and AD patients. They also tap into important aspects of executive function that have been demonstrated to be diminished in AD and MCI patients. Our tasks were carefully designed in order to be effortful, but still within the performance range of the three groups. In addition, we observed the predicted behavioural results, as well as a modulation of EEG coherence with trial type and working memory load for the experimental tasks.

Another important strength of these studies is that we collected multiple measures of neuropathology and cognition in the same participants. Furthermore, though the sample sizes were smaller for cortical thickness and PiB measures, these are the first studies to directly compare EEG coherence, cortical thickness, and PiB retention, and they provide several interesting avenues to follow-up in future research. In addition, we used the same participants across the three studies, allowing for direct comparison between studies. This is important because studies of functional connectivity use many different methods to calculate synchronization, use different electrode pairs, and use different frequency ranges, making comparison across studies difficult.

5.9 Future Directions

Though many studies have been published in recent years examining resting EEG coherence or synchronization in AD patients and MCI patients, we are still in the very early stages of understanding the how EEG coherence is affected over the course of dementia as well as the relationship between EEG coherence, neuropathology, cognition. There are many avenues to explore in future research in this area, some of which are discussed below.

First of all, to address some of the methodological limitations of the current studies, future studies using MEG or EEG source localization procedures would improve spatial

resolution and help to determine the specific brain regions between which synchronization is affected. Furthermore, as a follow-up to the preliminary findings reported here, future studies that measure EEG coherence, neuropathology, and cognition within a short time frame would be needed to provide confirmation of these results. In addition, studies with larger sample sizes should be aimed at replicating and extending these findings. Larger sample sizes would allow for a greater number of statistical comparisons, thus more electrode pairs and smaller frequency band windows could be examined. In addition, due to the overall slowing of the EEG signal in AD, a direct comparison of each frequency band may not be the most appropriate comparison to make for EEG coherence during the performance of a cognitive task. An alternative possibility is to determine which frequency range is most affected by the task in each group, and to then compare those frequency ranges across groups. Furthermore, it would be interesting to conduct a similar study with a larger number of trials in order to generate a sufficient number of incorrect trials for analysis. One might speculate that incorrect trials could possibly result from a transient "failure" of synchronization between brain regions, and more frequent failures may be present in AD and MCI patients, resulting in lower performance.

One particularly interesting area for future research is to further clarify the interrelationships between neuropathology, coherence, and cognition. This could be addressed more systematically, and with the inclusion of additional measures, such as proxy measures of cognitive reserve. This type of model could help to elucidate the role of individual differences in cognitive reserve as well as whether increases in coherence with increasing neuropathology are in fact compensatory in nature. Specifically, one could hypothesize several different relationships between EEG coherence and cognition, depending on the levels of neuropathology and cognitive reserve (CR): (1) neural efficiency, (2) hemispheric asymmetry reduction in older age (HAROLD), (3) neural compensation, (4) dedifferentiation, (5) early decline, and (6) late decline. Each of these hypotheses is described in further detail below.

First, according to the neural efficiency hypothesis, the more efficient you are at a task, the less networking activity is required (Barulli & Stern, 2013). Thus, a pattern consistent with neural efficiency might be expected in the case of low neuropathology and high CR, resulting in lower coherence and good performance. Second, HAROLD refers to the finding in older adults of a reduction in lateralization in the prefrontal cortex, such that older adults show greater bilateral activation in the prefrontal cortex in comparison to younger adults (Cabeza, 2002). A

pattern consistent with HAROLD might emerge in the case of low neuropathology and low CR, resulting in higher cross-hemisphere coherence and good performance. Third, neural compensation may occur in response to the onset of neuropathology, such that higher neuropathology accompanied by high CR results in higher coherence and good performance. Fourth, dedifferentiation may occur in cases of higher neuropathology and low CR, resulting in higher coherence and lower performance. Fifth, early decline may occur in cases where higher neuropathology and low CR results in a lower threshold of neuropathology that is required to produce lower coherence and poor performance. Finally, late decline represents the case where, regardless of the level of CR, when a certain threshold of neuropathology is reached, this results in lower coherence and poor performance. These hypotheses are summarized in Table 5.2.

One way to test the hypotheses presented above would be to create five groups based on the combination of neuropathology and cognitive reserve as outlined in Table 5.2, and compare the groups on measures of EEG coherence and cognitive performance. Only the dedifferentiation and early decline groups overlap in this regard, and the outcome for the coherence variables could help to distinguish between the dedifferentiation and early decline hypotheses. One might further test the compensatory model by examining various levels of task difficulty. Specifically, compensation may occur only at lower levels of task difficulty, whereas at higher levels of task difficulty, once the individual's neural capacity is reached, both coherence and performance would be reduced. In this instance, it would be useful to develop a task in which individual cognitive capacity can be determined in order to examine the effects on coherence when an individual's cognitive limit is reached. Furthermore, it might be interesting to test MCI patients under more difficult task conditions. In the current research, we did not find any evidence of decreased coherence in MCI patients, though we did find a pattern suggesting that MCI patients fail to increase coherence to the same extent as normal controls with increasing task demand. It could be hypothesized that if MCI patients were tested under more difficult task performance conditions, they may reach the limit of neural capacity and begin to show reduced coherence.

Compensatory hypotheses may also be examined using a longitudinal design, which would allow for the examination of within-individual changes in neuropathology, cognition, and cognitive performance over time, within the context of pre-existing levels of cognitive reserve. In this type of model, the effects of brain reserve could also be examined using premorbid

measures of brain structure. It may also be interesting to include measures of structural connectivity, such as diffusion tensor imaging, which has been found to be correlated with EEG coherence (Teipel et al., 2009). Thus, if individuals with high cognitive and brain reserve show increased EEG coherence concurrently with the onset of neuropathological burden, but prior to cognitive decline, this would provide evidence for a compensatory role of increases in coherence. Alternatively, individuals with low cognitive and brain reserve may show decreased coherence concurrent with the onset of both neuropathology and cognitive decline.

Longitudinal designs would also be useful in testing the effects of various interventions on EEG coherence and cognition, and particularly to examine the effects of intervention on EEG coherence during task performance. For example, the effects of treatment with cholinesterase inhibitors could be examined, as well as the effects of cognitive training, and aerobic exercise. Previous studies have found that medication improved local theta resting coherence, but not long range coherence in AD patients (Basar:2010hg; Yener, Güntekin, Öniz, & Başar, 2007), and both cognitive training (e.g., Lustig & Buckner, 2004; Nyberg et al., 2003) and aerobic exercise (e.g., Colcombe et al., 2004; McDowell, Kerick, Santa Maria, & Hatfield, 2003) have been found to improve behavioural performance and alter brain activation in older adults. Depending on individual differences on measures of neuropathology and cognitive reserve, coherence might be expected to either increase or decrease in response to these interventions. For example, in an individual with high cognitive reserve and a compensatory increase in coherence, interventions might be expected to lead to a decrease in coherence, due to increased neural efficiency. In contrast, in an individual with low cognitive reserve and lower coherence, interventions might be expected to lead to an increase in coherence.

The use of transcranial magnetic stimulation (TMS) could further elucidate the relationships between these factors. TMS is a non-invasive method of temporarily disrupting cortical activity by stimulation of the brain through the scalp. However, one must be cautious in the interpretation of the results of TMS studies in this area. For example, a compensatory increase in coherence might be expected to decrease as a result of intervention, due to a decreased need for the compensatory process, but TMS might also be expected to lead to a decrease in coherence in this case, due to a disruption of the ability to engage the compensatory process. However, in these two examples, performance would be expected to improve in the first case and decline in the second case. Thus, in the design of future studies testing the

interrelationships between these factors, it is extremely important not to consider one factor in isolation of the others, as an increase or decrease in coherence may have a different meaning depending on the other variables.

Finally, it is always important to know whether a given pattern of results is specific to the group being studied. It would be important for future research to examine EEG coherence in other groups of older adults with cognitive deficits, such as other forms of dementia or depression. Studies directly comparing AD patients with other groups would help to determine whether EEG coherence can be used to distinguish between different types of dementia or between AD and other neuropsychiatric disorders.

5.10 Conclusion

Overall, the results of this dissertation support the hypotheses of functional disconnection in AD patients and functional compensation in MCI patients during the performance of executive function tasks. Executive functions require multiple types of information to be integrated quickly and simultaneously, and thus depend on the integrity of cortico-cortical tracts. These results point to an inconsistent relationship between functional connectivity and performance on tasks of executive function in normal elderly controls, MCI patients, and AD patients. Future research aimed at clarifying the role of factors such as cognitive reserve in potentially moderating the relationship between functional connectivity and cognition should provide additional insight into how changes in neural networks support or hinder executive functioning within the context of the neuropathology of AD.

Table 5.1.

Correlations Between Neuroimaging Measures and Neuropsychological Test Performance

	Normal Elderly Controls			Mild Cognitive Impairment			Alzhiemer's Disease		
	Variables	***r***	***p***	**Variables**	***r***	***p***	**Variables**	***r***	***p***
Cortical Thickness	**Middle Frontal Gyrus & Stroop Time**	**-.864**	**.012**						
				Anterior Cingulate Cortex & Stroop Time	.626	.039	**Anterior Cingulate Cortex & Stroop Errors**	**-.890**	**.017**
	Superior Parietal Lobule & MoCA	**.791**	**.034**						
	Superior Parietal Lobule & CVLT Delayed Recall	**.757**	**.049**						
	Superior Parietal Lobule & Stroop Time	**-.809**	**.027**						
PiB Retention	Superior Frontal Gyrus & Stroop Time	.744	.014	Superior Frontal Gyrus & Stroop Time	.730	.040	Superior Frontal Gyrus & LNS	-.880	.021
	Middle Frontal Gyrus & Stroop Time	.695	.026				Middle Frontal Gyrus & MoCA	-.783	.037
	Anterior Cingulate Cortex & Stroop Time	.671	.034						
				Superior Parietal Lobule & Stroop Time	.711	.048	Superior Parietal Lobule & MoCA	-.916	.004
Resting Coherence							**Delta F3-F4 & Hayling Test Errors Scaled Score**	**.779**	**.002**
							Theta F3-F4 & Hayling Test Errors Scaled Score	**.713**	**.006**
							Alpha F3-F4 & Hayling Test Errors Scaled Score	**.786**	**.001**
							Beta F3-F4 & CVLT Delayed Recall	**.700**	**.004**
	Gamma F3-F4 & Hayling Test Errors Scaled Score	-.485	.012	**Gamma F3-F4 & Stroop Time**	**-.595**	**.032**	**Gamma F3-F4 & CVLT Delayed Recall**	**.796**	**<.001**
							Delta P3-P4 & LNS	**.617**	**.019**
							Theta P3-P4 & Hayling Test Time	.651	.016
							Theta P3-P4 & Hayling Test Errors Scaled Score	**.575**	**.040**
							Alpha P3-P4 & Hayling Test Errors Scaled Score	**.813**	**.001**
							Beta P3-P4 & Hayling Test Time	.601	.030
							Gamma P3-P4 & LNS	-.667	.018
							Theta F3-P3 & Hayling Test Time	.723	.005
	Alpha F3-P3 & CVLT Delayed Recall	-.415	.035				Alpha F3-P3 & Stroop Errors	.538	.047
	Alpha F3-P3 & Hayling Test Time	**-.398**	**.049**				Alpha F3-P3 & Hayling Test Time	.589	.034
	Beta F3-P3 & CVLT Delayed Recall	-.458	.019	Beta F3-P3 & LNS	-.582	.047	**Beta F3-P3 & CVLT Delayed Recall**	**.681**	**.005**
							Gamma F3-P3 & CVLT Delayed Recall	**.648**	**.009**
Go/No-go Coherence	**Delta F3-F4 & MoCA**	**.409**	**.038**						
(No-go minus Go)	Beta F3-F4 & Stroop Errors	.552	.003						
	Gamma F3-F4 & Stroop Errors	.436	.026						
							Delta P3-P4 & CVLT Delayed Recall	**.566**	**.028**
	Theta P3-P4 & Hayling Test Time	.404	.045				**Theta P3-P4 & Hayling Test Time**	**-.699**	**.008**
							Theta P3-P4 & Hayling Test Errors Scaled Score	**.619**	**.001**
				Alpha P3-P4 & LNS	**.600**	**.039**			
	Beta P3-P4 & Hayling Test Time	**-.450**	**.024**	Beta P3-P4 & Stroop Time	.555	.049			
				Beta P3-P4 & Stroop Errors	.561	.046			
				Gamma P3-P4 & LNS	**.760**	**.004**			
	Gamma F3-P3 & Hayling Test Errors Scaled Score	-.437	.026						

Table 5.1 continues...

Table 5.1 (cont.)

Correlations Between Neuroimaging Measures and Neuropsychological Test Performance

	Normal Elderly Controls			Mild Cognitive Impairment			Alzhiemer's Disease		
	Variables	***r***	***p***	**Variables**	***r***	***p***	**Variables**	***r***	***p***
N-back Coherence	Delta F3-F4 & CVLT Delayed Recall	-.463	.020						
(1-back minus 0-back)	Theta F3-F4 & Stroop Errors	.445	.026						
				Alpha F3-F4 & LNS	-.734	.001			
	Beta F3-F4 & Trails B/A	.470	.027	**Beta F3-F4 & Hayling Test Time**	**-.520**	**.027**	Beta F3-F4 & Hayling Test Errors Scaled Score	-.766	.001
	Gamma F3-F4 & Stroop Errors	**-.398**	**.049**						
	Delta P3-P4 & Stroop Time	.438	.029	**Delta P3-P4 & Hayling Test Time**	**-.474**	**.047**	**Delta P3-P4 & LNS**	**.566**	**.044**
	Alpha P3-P4 & Hayling Test Time	**-.507**	**.012**						
	Gamma P3-P4 & Trails B/A	**-.458**	**.032**						
	Delta F3-P3 & CVLT Delayed Recall	-.432	.031				Delta F3-P3 & CVLT Delayed Recall	-.531	.034
				Alpha F3-P3 & CVLT Delayed Recall	-.440	.046			
	Beta F3-P3 & MoCA	-.442	.024				Beta F3-P3 & Hayling Test Errors Scaled Score	-.623	.017
	Beta F3-P3 & Trails B/A	.686	<.001						

Note. For ease of interpretation, a positive relationship between neuroimaging measures and better performance on neuropsychological tests is indicated in bold.

Table 5.2

Hypotheses for the Interaction Between Neuropathology, Cognitive Reserve, Functional Neural Networks, and Cognition

	Pathology	CR	Coherence	Performance
Efficiency	↓	↑	↓	↑
HAROLD	↓	↓	↑	↑
Compensation	↑	↑	↑	↑
Dedifferentiation	↑	↓	↑	↓
Early Decline	↑	↓	↓	↓
Late Decline	↑↑	↑	↓	↓

Note. CR = cognitive reserve. HAROLD = hemispheric asymmetry reduction in older adults.

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