Summer 2018

Dissociating Alzheimer's Disease from Amnestic Mild Cognitive Impairment using Time-Frequency Based EEG Neurometrics

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Thesis here presented to the Graduate Faculty of The College of William & Mary in Candidacy for the Degree of
Master of Arts

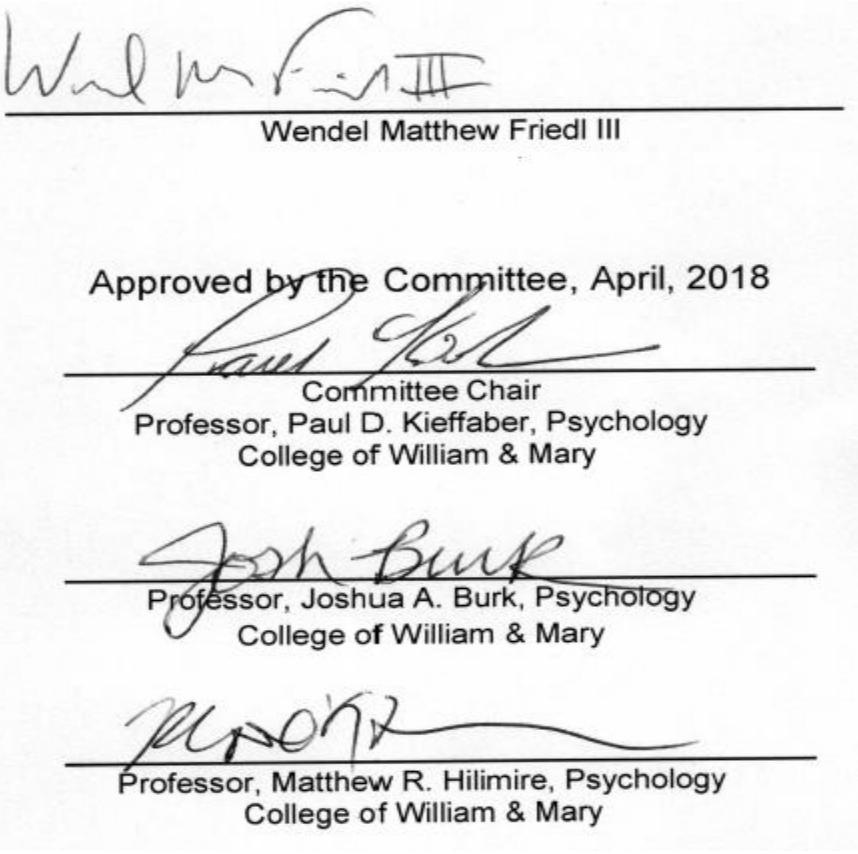
Psychological Sciences

College of William & Mary
May 2018

APPROVAL PAGE

Thesis here is submitted in partial fulfillment of
the requirements for the degree of

Master of Arts



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ABSTRACT

Alzheimer's Disease (AD), already the most common cause of dementia, is a rapidly escalating worldwide health concern thanks to increasing life expectancies and aging populations. This work explores the utility of using magnitude (ERSP), phase angle (ITPC), and cross-frequency coupling (PAC) indices derived from electroencephalogram (EEG) recording using spectral decomposition as unique biomarkers of AD and amnestic mild cognitive impairment (aMCI), respectively. The experimental protocol was a visual oddball discrimination task conducted during a brief (approximately 20 minute) recording session. Participants were 60 older adults from an outpatient memory clinic diagnosed with either aMCI (n=29; M=73.0; SD=9.32) or AD (n=31; M=78.29; SD=8.28) according to NIA-AA criteria. Results indicate that ITPC values differ significantly between AD and MCI groups. Findings contribute to a growing body of literature seeking to document illness-related abnormalities in time-frequency EEG signatures that may serve as reliable indicators of the pathophysiological processes underlying the cognitive deficits observed in AD and aMCI-afflicted populations.

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ACKNOWLEDGEMENTS

I sincerely thank Professors Josh Burk and Matt Hilimire for their time, assistance, and valuable feedback both in the preparation of this document as well as in the classes I have had the pleasure to take from them. I also would like to recognize the contributions of my advisor, Professor Paul Kieffaber, without whose expertise in the fields of EEG analysis and computer programming this effort would not have been possible.

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Dissociating Alzheimer's Disease from Amnestic Mild Cognitive Impairment Using Time-Frequency Based EEG Neurometrics

Alzheimer's Disease (AD) is a progressive, incurable neurodegenerative disorder characterized chiefly by memory impairment early in the course of the disease (Albert & Moss, 1999), eventually giving way to a host of behavioral and cognitive deficits which prevent those afflicted from autonomously performing most activities of daily living (ADLs; McKhann et al., 2011). Already the most common form of dementia (Buckner, 2004; Jiang, Yu, Tian, & Tan, 2013), the number of those suffering from AD is projected to reach epidemic proportions in the coming decades (Brookmeyer, Johnson, Ziegler-Graham, & Arrighi, 2007) as the proportion of individuals aged 65 and older constituting the worldwide population inexorably climbs. The development of biomarkers - objective measures of a pathogenic process that can be used to gauge risk for or track the progression of a disease (Hampel et al., 2010) – of AD has enabled the identification of at-risk individuals prior to the onset of overt cognitive and behavioral symptoms in research settings, yet still only around one-quarter of those afflicted with AD are receiving a diagnosis (Prince, 2016). No biomarker or set of biomarkers has/have yet been sufficiently validated for clinical application, and currently accepted biomarkers for research study inclusion are too costly, invasive, and/or require too much specialized equipment to be economically or ethically feasible on a large scale (Scally, Calderon, Anghinah, & Parra, 2016). Additionally, current AD biomarker research efforts largely fail to investigate potential measures that may aid clinicians in distinguishing between mild cognitive impairment (MCI) and AD, focusing on the distinction between age matched control and AD-afflicted populations. As MCI often presages the eventual

development of AD, objective measures to aid clinicians in distinguishing between MCI and AD and that could serve, post-diagnosis, as indices of the efficacy and, eventually, the effectiveness of treatment interventions would be an enormous medical and societal benefit.

The current study tests for concordance between established cognitive and physiological indicators of AD and MCI and measures of the magnitude, phase, and phase-amplitude coupling (PAC) of frequencies derived from electroencephalogram (EEG) recording using spectral decomposition. Participants performed a visual oddball discrimination task (Hillyard & Kutas, 1983), in which occasional, relevant 'target' stimuli must be detected in a train of frequent, irrelevant 'non-target' stimuli. Note that, despite advances in neuroimaging and genetic risk profiling, definitive confirmation of an AD diagnosis can still only be made via post-mortem neuropathological examination to confirm the presence of neurofibrillary tangles (NFTs) and senile plaques (Dauwels, Vialatte, & Cichocki, 2010; Hyman et al., 2012); however, hereafter this document will refer to probable but unconfirmed AD simply as AD. Additionally, all references made to AD throughout this paper – unless explicitly noted – refer to late-onset (age 65 or older) AD. Early-onset AD, which constitutes only around 1 - 5.5% (Sassi et al., 2014; Zhu et al., 2015) of the total patient population, exhibits a pattern and time course of cognitive impairment distinct from the far more common, late-onset AD cases (Smits et al., 2012). As EEG diagnostic indicators similarly show a differential pattern of abnormalities in early, as compared to late, onset AD (De Waal et al., 2011), generalizing findings from the current sample population, which does not contain any individuals diagnosed as early-onset, would be unwarranted.

The most recently suggested diagnostic criteria from the National Institute on Aging/Alzheimer's Association (NIA-AA) defines three distinct stages of AD: Preclinical AD, mild cognitive impairment (MCI) due to AD, and probable AD (Albert et al., 2011; Jack et al., 2011; McKhann et al., 2011; Sperling et al., 2011). This tripartite conceptualization of AD formalizes the evolving understanding of the disease as a gradient of progressive neural degeneration, not simply an all-or-none phenomenon. Preclinical AD individuals are asymptomatic, presenting only biomarker-based evidence of neurological disorder (Sperling et al., 2011). Observable cognitive and behavioral impairments characterize the MCI phase of AD, with this stage of the disease representing a transitional state between normal aging and AD. Amongst MCI patients, approximately 10–25% of individuals transition to AD within a given one-year period (Petersen, 2000; Petersen et al., 1999; Petersen et al., 2001). Crucially, clinical symptoms brought on by AD pathology often do not manifest until years after the onset of neurodegeneration (Braak, Braak, & Bohl, 1993; Sperling et al., 2011). By the onset of clinically diagnosable AD, significant and irreversible tissue damage is likely to have occurred, accompanied by detectable atrophy of brain mass compared to both MCI and healthy controls (Hua et al., 2008). Current clinical trials of preventative drugs likely begin too far along in the timeline of AD, when significant and irreparable tissue damage is already likely to have occurred (Godyń, Jończyk, Panek, & Malawska, 2016). As noted by Cummings and colleagues (2007), both treatment and preventative therapies aimed at altering the pathogenesis of the disease are more likely to be effective if begun at pre-dementia stages.

Given the progressive nature of AD and the temporal separation between the beginning of neural degeneration and the onset of overt behavioral deficits (Price & Morris, 1999), there is widespread agreement on the pressing need for reliable, sensitive, and specific biomarkers of AD and MCI, with both the International Working Group (IWG; Dubois et al., 2007, 2010) and the National Institute on Aging/Alzheimer's Association (NIA-AA; Albert et al., 2011; Jack et al., 2011; McKhann et al., 2011; Sperling et al., 2011) recommending continued development and verification of such measures. Current research recommendations center on using multi-modal biomarkers including genetic, structural neuroimaging, and functional neuroimaging (Dubois et al., 2007; McKhann et al., 2011), while largely ignoring neurophysiological methods such as EEG. Some workgroups (e.g. Jackson & Snyder, 2008; Yener & Başar, 2013) have pointed out that EEG possesses many desirable features that recommend its inclusion in the search for optimal sets of biomarkers of AD and MCI. As noted by Ashford, Rosen, Adamson, and Bayley (2011):

> In many ways EEG offers an ideal method for assessing brain function. Its exquisite temporal resolution can track brain activity in the millisecond time domain characteristic of neuronal activity in the cortical substrate. It is entirely noninvasive and employs no ionizing radiation. It records both excitatory and inhibitory signals directly rather than secondary hemodynamic processes. It also is inexpensive (p. 375).

Such a feature set contrasts, in many respects, with current biomarkers commonly used as inclusion criteria for research studies.

Biomarkers of Alzheimer's Disease

Since Alois Alzheimer first documented their presence during autopsy of a patient suffering from the disease that would later bear his name, intracellular plaques and extracellular NFTs have become the telltale, physically defining features of AD *(*Golde, Eckman, & Younkin, 2000*;* Mattson, 2004*;* Walsh and Selkoe, 2004*)*. It has long been suggested that aggregation of amyloid beta (Aβ) is the initiating factor in the pathogenic chain of AD (Hardy & Selkoe, 2002), with the popular (although not uncontroversial; see, e.g., Herrup, 2015) amyloid cascade hypothesis positing that Aβ accumulation and plaque formation drives the formation of NFTs of hyperphosphorylated tau protein that correlate strongly with the progressive neuronal dysfunction observed in AD (reviewed in Holtzman, Morris, & Goate, 2011).

Imaging the toxic Aβ peptides that comprise the extracellular plaques characteristic of AD using positron emission tomography (PET) has enabled the identification of Aβ deposits far preceding the commencement of overt cognitive decline, with a recent study (Rodriguez-Vieitez et al., 2016) showing fibrillar Aβ plaque accumulation characteristic of AD appearing as much as 17 years before the expected onset of overt clinical symptoms. Aβ plaque accumulation far pre-dating the onset of clinical AD symptoms has become well established (e.g. Bateman et al., 2012; Mintun et al., 2006; Sperling et al., 2011), but the fact that non-demented elderly subjects often display significant Aβ plaque burden (Quigley et al., 2011) suggests that such a measure alone cannot provide an accurate early diagnosis that is unique to AD. Additionally, PET imaging is not widely available, is quite expensive, and The National

Research Council (NRC, 2007) reports that demand for the radionucleotides used in PET scans is likely to far outstrip the available supply in the coming decades.

Measuring, via cerebrospinal fluid (CSF) draw, levels of Aβ along with levels of phosphorylated tau proteins (P-tau and T-tau) that form intracellular NFTs is an invasive procedure requiring lumbar puncture with a catheter. Both Aβ and tau levels tend to remain relatively stable over time (Blennow, Mattsson, Schöll, Hansson, & Zetterberg, 2015; Blennow et al., 2007), which is a desirable quality for gauging the efficacy of treatment interventions but suggests that these measures are not ideally suited to gauge disease progression in *de novo* individuals.

For nearly two decades, multiple genes have been associated with increased AD risk (Karch, Cruchaga, & Goate, 2014). Certain mutations in amyloid precursor proteins (APPs) presenilin-1 (PSEN 1) and presenilin-2 (PSEN 2) are known to cause early-onset AD (reviewed in Guerreiro, Gustafson, & Hardy, 2012), and a specific isoform of Apolipoprotein E (APOE), APOEε4, indicates a substantially increased risk for both early- and late-onset AD (reviewed in Guerreiro, Gustafson, & Hardy, 2012). However, as previously noted, early-onset AD comprises only a small fraction of the total AD population, and furthermore, only 50% of individuals with AD carry an APOEε4 allele (Karch, Cruchaga, & Goate, 2014). As genetic composition is fixed throughout the lifetime, genomic biomarkers appear better suited to identifying at-risk individuals than to either detecting the actual presence or gauging the progression of AD-related pathology.

Structural magnetic resonance imaging (MRI) studies reliably find pronounced atrophy of the hippocampus and surrounding areas of temporal cortex in patients with AD (e.g., Jack, Petersen, O'Brien, & Tangalos, 1992; Killiany & Albert, 1993; reviewed in Jack & Petersen, 2000), as well as hippocampal shape deformation (Csernansky et al., 2000). Cell loss in areas of the medial temporal cortex including the hippocampus likely contributes significantly to impaired memory performance in individuals with AD (reviewed in Albert, 1997), as the medial temporal region is important to both working (Ranganath, 2006) and long-term (Squire, 1992) memory. Temporal lobe atrophy revealed through structural MRI also appears to be a viable diagnostic tool with which to gauge the progression of MCI and AD, as temporal lobe volume decreases in proportion to disease severity (Jack et al., 2011) and has been able to predict the conversion from MCI to AD (DeCarli et al., 2007). On the downside, MRI imaging is expensive, with costs generally spanning from several hundred to several thousand dollars per session, and the technology requires substantial investment on the part of a research or medical facility both to purchase an MRI scanner and to properly shield surrounding areas from the extreme magnetic forces employed by this type of imaging.

Despite its long history (Berger, 1929), low costs of operation, and non-invasive nature, EEG has to date failed to receive widespread clinical acceptance in the context of AD and MCI diagnosis and/or progression monitoring. Yet, among all potential biomarkers of AD so far discussed, EEG alone possesses sufficient temporal resolution to measure synaptic activity in real-time (Cook & Leuchter, 1996). As AD has been conceptualized as (among many things) primarily a disorder of synaptic plasticity (Klein, 2006; Selkoe, 2002; Walsh et al., 2002), a measure sensitive to changes in synaptic

performance could provide an important, unique metric by which to gauge progression of the underlying pathogenic processes of AD. Altered synaptic plasticity far preceding the appearance of Aβ containing plaques and brain atrophy in animal models (Hsia et al., 1999; Lesné et al., 2006; Rowan, Klyubin, Cullen, & Anwyl, 2003) further supports the notion that EEG-derived measures could be even more sensitive to early functional alterations occurring in AD than is volumetric assessment of temporal lobe atrophy via structural MRI (Olichney, Yang, Taylor, & Kutas, 2011). However, some studies indicate that the accuracy with which EEG derived measures can correctly identify AD patients from healthy controls is both poor and highly variable (Stam et al., 1996), and large inter-individual variation in these readings often prevents detection of AD at the individual level (Yener & Başar, 2013). Decomposing the observed EEG signal into its constituent frequency bands and examining stimulus responses within these individual bands may provide a means of improving the accuracy and specificity with which AD and MCI can be detected and distinguished, as these narrow band frequency responses may better reflect specific aspects of cognitive function (Başar, 2004).

Time-frequency EEG measures of Brain Oscillations

As a sweeping generalization, the rhythmically fluctuating, periodic and/or quasi-periodic signal observed in EEG recordings can be said to reflect the summated dendritic post-synaptic potentials of millions to billions of – primarily – cortical pyramidal neurons (Buzsáki, Anastassiou, & Koch, 2012; da Silva, 2013). The observed magnitude of the electrical fields caused by transmembrane potentials created as charged ions flow into and out of neurons constitute what Buzsáki (2002) terms the

current generator portion of the signal. Other mechanisms - or rhythm generators (Buzsáki, 2002) - give rise to the timing and frequency of the signal and are held to be especially important in coordinating firing patterns in neuronal networks (Singer, 1999). Inhibitory interneurons play a particularly prominent role in timing rhythmic activity in the brain (Mann & Paulsen, 2007), as their dense interconnections within local networks allow them to influence numerous neurons, creating cyclical fluctuations between high and low-probability spiking behavior (Traub et al., 2002). Such alternation between increased and decreased action potential probability entrains principle neurons into synchronized firing patterns (Mann & Paulsen, 2007) typically described as neural oscillations, or – more colloquially – brain rhythms.

Once widely regarded as mere epiphenomena, oscillations are increasingly viewed as playing a functionally meaningful role in cognitive processes (e.g. Fries, Reynolds, Rorie, & Desimone, 2001; Ward, 2003). The timing function provided by oscillations, as entrained neurons alternate between periods of excitation and inhibition, opens windows of opportunity within which communication between neurons is maximally effective (Fries, 2005). Notably, such facilitation of communication through temporal coordination can be achieved even in lieu of an increase in overall spiking behavior, by grouping spikes into compressed time windows particularly effective at activating downstream neurons (Azouz & Gray, 2000; Salinas & Sejnowski, 2001). Oscillatory activity can be subdivided into the actions of *true oscillators* – neurons capable of self-sustained rhythmic firing independent of synaptic input – versus that of *resonators*, or neurons that are preferentially induced to fire rhythmically in response to oscillatory synaptic input at specific frequencies (Llinas, 1988). Neurons in different

brain regions can exhibit resonant frequency preference towards oscillations of multiple frequencies (Jacobs, Kahana, Ekstrom, & Fried, 2007) with neocortical pyramidal neurons, for example, displaying both low and high frequency resonance (Hutcheon & Yarom, 2000). However, as distinguishing between true oscillators and resonators involves features detectable at the single-cell level of observation (Llinas, 1988), such a fine-grained distinction will not be made in the present work and all references to oscillations or oscillatory activity made herein may be more accurately taken to mean the activity of neuronal populations comprising true oscillators and/or resonators.

Filtering continuous EEG data into its constituent sinusoidal components reveals the underlying frequency content of the signal, which can then be displayed as a distribution of signal power over discrete frequency bands (see Figure 1). Not all rhythmic brain activity reveled by EEG is oscillatory in nature (Miller, Honey, Hermes, Rao, & Ojemann, 2014), with the croquet-hoop shaped positive deflections of mu-rhythms (~9-11 Hz) representing one exception (Gross, 2014), as they fail to exhibit a clear spectral peak. Neural oscillatory activity is, however, the most prominent feature of EEG (Cohen, 2017), and patterns and changes in these narrow-band signals has recently begun garnering significant attention in studies of cognitive dynamics in both healthy and clinical populations. Oscillatory activity as fast as 600 Hz has been identified in human EEG (Curio, 1999; Curio et al., 1994), but the frequency bands most often studied are delta (>1 – 4 Hz), theta (4 – 8 Hz), alpha (8 – 12 Hz), beta (12 – 20 Hz) and gamma (20 – 80 Hz), which have been termed the natural frequencies of the brain (Başar, Başar-Eroglu, Karakaş, & Schürmann, 2001). Any signal, including indicators of brain oscillations, can be fully described by its spectral properties,

consisting of the amplitude (or power, the square of the amplitude), frequency, and phase of the observed signal. Broadly: Frequency can be taken as an indicator of the speed, phase activity as a measure of the timing, and power as a measure of the strength of the underlying neuronal activity (Cohen, 2014). Importantly, these three signal properties provide largely independent information, save for a reciprocal relationship between amplitude and frequency, with amplitude decreasing along with increasing signal frequency in a roughly 1/f (amplitude = 1/frequency) manner (Freeman, Rogers, Holmes, & Silbergeld, 2000).

As EEG observed at the scalp represents a summed total of the activity of large neuronal populations (Başar, 1980; Steriade, Gloor, Llinas, da Silva, & Mesulam, 1990), amplitude increases can be caused by either more neurons with the same degree of inter-neuronal synchrony or the same number of neurons exhibiting a higher degree of inter-neuronal synchrony (Herrmann & Demiralp, 2005). Thus, including phase information in the analysis of cognitive processing gives a more complete picture of the underlying temporal dynamics of the involved oscillatory processes “stripped” of the influence of amplitude (Cohen, 2014; Roach & Mathalon, 2008). Oscillatory activity in the brain can exhibit three types of synchrony: Inter-neuronal, inter-electrode, and/or inter-trial (Herrmann & Demiralp, 2005). Event-related phase consistency across trials at a single electrode is especially important when studying event-related oscillations (EROs; Herrmann & Demiralp, 2005), and will be the only measure of phase synchronization discussed in this paper. As a definitional note, inter-trial phase clustering (ITPC) - also variously referred to as phase-locking value, phase-locking factor, phase resetting, phase coherence, inter-trial phase coherence, and/or cross-trial

phase coherence (Cohen, 2014) - will be the term used to describe this type of neuronal synchronization throughout the present work. By convention, *coherence* usually denotes phase synchronization between two separate recording sites (electrodes) (Andrew & Pfurtscheller, 1996), while *locking* describes synchronization at a single-site (electrode) across trials (Roach & Mathalon, 2008): However, the use of the term ITPC appears to be becoming somewhat standard practice in the EEG literature of late. The term *synchronization* itself has manifold uses in the extant literature: Synchronization can generally describe high amplitude, low frequency activity in the EEG (Steriade, Gloor, Llinas, Da Silva, & Mesulam, 1990); synchronization can be a measure of the relation between the temporal structure (rhythm) of signals regardless of signal amplitude (Varela, Lachaux, Rodriguez, & Martinerie, 2001); and event related synchronization (ERS) is sometimes used to denote an increase in power from baseline within a given frequency band (Pfurtscheller, 1992).

EEG as a Potential Biomarker of AD

The earliest and most numerous studies (e.g. Başar & Güntekin, 2008; Brenner et al., 1986; Coben, Danziger, & Berg, 1983; Duffy, Albert, & McAnulty, 1984) investigating potential EEG indices of AD utilized mainly resting state (spontaneous) EEG, in which participants sit motionless for several minutes while having brain activity recorded. These studies reliably show a pronounced slowing of the EEG signal in individuals with AD (Czigler et al. 2008; Dauwels, Vialatte, & Cichocki, 2010; Moretti et al. 2009; reviewed in Jackson & Snyder, 2008), with a higher proportion of signal power manifesting in lower frequency bands and continued slowing that progresses along with

advancing cognitive impairment (Bennys, Rondouin, Vergnes, & Touchon, 2001; Jeong, 2004; Schreiter-Gasser, Gasser, & Ziegler,1994). While the resting state testing protocol has the advantage of being undemanding for participants and has demonstrated impressive discriminating performance in some studies, results involving this method are mixed. For example: Lehmann and colleagues (2007) reported resting state measures that differentiated mild AD subjects from healthy controls with 85% sensitivity and 78% specificity, while a meta-analysis of resting state studies (Jelic & Kowalski, 2009) showed that classification accuracies between AD and controls ranged between 2.3% and 38.5%, with diagnostic odds ratios (a ratio of the odds of the test being positive if an individual has a disease to the odds of the test being positive if that individual does not have the disease) between 7 and 219. Such variability may be partially attributable to the fact that, in the context of a never silent brain, "the alleged 'resting state' is ill defined and difficult to control" (Gross, 2014, p.59).

As the testing protocol typically lacks any type of cognitive or sensory stimulation, resting state recordings may not be sensitive enough to produce significant group differences in spectral EEG metrics (Günther et al., 1993). In contrast to recording spontaneous or resting state activity, event-related (ER) paradigms measure the electrical response of the brain to a stimulus, typically to an infrequently presented target stimulus nested within a sequence of similar but more frequent stimuli in an oddball paradigm (Başar, Başar-Eroğlu, Güntekin, & Yener, 2013). Consequently, it has been suggested that ER responses can provide a more accurate evaluation of AD (Polich & Herbst, 2000). Detection of oddball stimuli involves both sensory mechanisms and cognitive processes including attention, perception, learning, and working memory

(Halgren, Boujon, Clarke, Wang, & Chauvel, 2002; Klimesch et al., 2006; Rektor et al., 2004). This set of cognitive mechanisms is notable in that it encompasses many of the executive functions most affected by AD (Collette, Van der Linden, & Salmon, 1999; Lafleche & Albert, 1995). Intuitively, directly probing an impaired functional process such as memory appears much more likely to reveal specific, rather than general, patterns of neural dysfunction corresponding to the cognitive deficits seen in AD and MCI patient populations.

Event-related EEG experimental protocols elicit both induced and evoked oscillatory responses: Induced responses – also called event-related spectral perturbations (ERSPs; Makeig, 1993) - follow, but are not phase-locked to, sensory stimuli (Engel, König, Kreiter, Schillen, & Singer, 1992), while earlier occurring evoked oscillatory responses consistently and precisely phase synchronize to a stimulus (Herrmann & Demiralp, 2005; Tallon-Baudry & Bertrand, 1999). Evoked EEG activity emerges automatically in response to audio, visual, or somatosensory stimuli of sufficient magnitude (Herrmann, Grigutsch, & Busch, 2005) and typically occurs within the first 200 ms following stimulus onset (Roach & Mathalon, 2008). Accordingly, event-related activity revealed by spectral decomposition of the EEG signal can be further sub-divided into obligatory responses elicited by simple sensory stimuli (sensory-related oscillations; SROs) and event-related oscillations (EROs) that reflect higher cognitive processing (Yener & Başar, 2010). Evoked and induced (ERSP) responses are also - more descriptively - referred to as phase locked and non-phase locked activity, respectively. Activity that is both time and phase locked shows up in the familiar event-related potential (ERP), while the time-domain averaging process involved in creating

ERPs cancels out all activity that is not tightly time and phase locked to stimulus onset (Makeig, 1993). To obtain a picture of non-phase locked activity, the EEG signal is first transformed into the frequency domain, using methods such as Morlet wavelet convolution or bandpass filtering, prior to averaging across trials (Tallon-Baudry & Bertrand, 1999). EROs enable examination of parallel processing activity in the brain by revealing associations between simultaneously occurring processes taking place at different frequencies (Lisman & Buzsáki, 2008), yielding a more detailed picture of event-related brain activity relative to ERPs (Roach & Mathalon, 2008). Thus, it has been suggested that examining the full spectra of EEG activity generated in response to cognitive tasks affords the clearest and most comprehensive assessment of damaged cognitive networks in cases such as AD (Başar, Başar-Eroğlu, Güntekin, & Yener, 2013), a level of detail highly desirable when attempting to make a fine-grained distinction such as that between the conditions of MCI and AD. Supporting the enhanced diagnostic potential of time-frequency based measures, Ford and colleagues (2008) found both phase and power measures induced by an oddball task to be more sensitive to schizophrenia than the P300 component of the ERP.

As empirical studies associating event-related oscillatory activity with cognitive functions accumulate, two frequency bands particularly implicated in the study of memory processes and psychopathological impairment of memory are theta (4-8 Hz) and gamma (30-80 Hz), along with – increasingly – studies of their association.

Theta. Of all EEG frequency bands, theta has been the most consistently found to relate to human memory performance (Klimesch et al., 2005), especially during the

active maintenance of items in working memory (WM; Sauseng, Klimesch, Schabus, & Doppelmayr, 2005). While the majority of theta activity recorded at the scalp is likely to originate from cortical sources, as areas such as cingulate and perirhinal cortices have been found to be the main drivers of amplitude fluctuations in extracellular recordings (Buzsáki, 2002), depth electrode recordings in animals indicate that theta oscillations are largest in amplitude and most regular in frequency in the hippocampus (Buzsáki, 2002). Theta activity originating in the hippocampus is thought to help time interactions between prefrontal cortex and hippocampus during memory-guided action selection (Hasselmo, 2005), and the theta and delta frequency ranges are the primary constituents of the P300 ERP component (Başar-Eroglu, Başar, Demiralp, & Schürmann, 1992) commonly linked to functions such as memory matching, attention, and decision-making. Importantly, alterations in delta and theta activity are also consistently found to be abnormal in studies of AD pathology utilizing the oddball paradigm (Caravaglios, Costanzo, Palermo, & Muscoso, 2008; Yener, Güntekin, & Başar, 2008).

While consistently linked, the relationship between theta and memory performance appears to be highly nuanced and at least partially non-linear (Klimesch, 1999). Theta power is increased during memory encoding (Başar, Başar-Eroğlu, Karakaş, & Schürmann, 2000; Klimesch, 1999; Paré, Collins, & Pelletier, 2002) and increases along with the number of items concurrently maintained in working memory (Jensen & Tesche, 2002). However, findings by Klimesch (1999) indicate differential patterns of theta activity for good versus poorly performing subjects in a cognitive task: Good performers tend to exhibit lower pre-stimulus baseline (tonic) theta band power

along with highly increased event related theta power relative to baseline, while these values are reversed in poor performers. In addition to power, consistent theta band phase locking may contribute meaningfully to successful episodic memory encoding, as precise timing of neuronal spiking with respect to ongoing theta may predict successful encoding of memories even in the absence of a net increase in hippocampal firing rate (Rutishauser, Ross, Mamelak, & Schuman, 2010). Theta is also held to represent different aspects of episodic memory retrieval depending upon the time window in question, with early activity (~100-400 ms post-stimulus) reflecting either encoding of new information or recall of old information, and late activity (after ~500 ms) indicating evaluation of an episodic trace (Klimesch et al., 2005). Significant increases in theta power during the encoding phase corresponds to items that are later successfully recalled (Klimesch, Doppelmayr, Pachinger, & Ripper, 1997; Klimesch, Doppelmayr, Russegger, & Pachinger, 1996), while late increases in theta reflect the increasing cognitive demands associated with evaluating weaker memory traces (Klimsche et al., 2005). The time course of theta activity has also been shown to differentiate between the conscious states of knowing versus remembering items (Klimesch et al., 2001). Klimesch and colleagues (2001), in line with behavioral results indicating that familiarity judgements are made more rapidly than are judgements requiring recall of specific episodic information (Düzel, Yonelinas, Mangun, Heinze, & Tulving, 1997), found familiar (known) words to elicit the largest theta increase in the early (200-375 ms) post-stimulus period while explicitly remembering recently presented words coincided with the largest increases in late-period (500-625 ms) theta power. In the oddball paradigm, theta activity is prolonged for target as compared to standard stimuli (Başar-Eroglu,

Başar, Demiralp, & Schürmann, 1992; Demiralp & Ademoglu, 2001; Yordanova & Kolev, 1998).

Consistent with the differing pattern of theta power changes observed for good versus bad memory performers amongst healthy subjects (Klimesch, 1999), Missonnier and coworkers (2006) found progressive MCI cases to exhibit significantly lower event-related theta power over all electrode sites compared to stable MCI cases. At least two studies (Hogan, Swanwick, Kaiser, Rowan, & Lawlor, 2003; Karrasch et al., 2006) have failed to find the expected differences between AD patients and controls in the theta range during memory recall. Karrasch and colleagues (2006) additionally found similar theta power increases during encoding amongst controls and AD patients, while MCI patients exhibited decreased event-related theta power. Such unexpected similarities between controls and AD patients may indicate a non-linear relationship between theta power and disease progression, may have been driven by temporal blurring of the low-frequency signal due to the parameters of the wavelets used for spectral decomposition (Karrasch et al., 2006), or might reflect the activation of different neuronal networks in the controls and the AD patients (Karrasch et al., 2006). Another possibility is that Acetylcholinesterase inhibitor (AChEI) medication status – not mentioned in either study – could have produced theta-band profiles in medicated AD patients that resembled those of healthy control subjects. Regarding this last possibility, Yenner and coworkers (2007) found event-related theta phase locking in AChEl treated AD patients to be two times higher than the values observed in untreated AD subjects, with medicated individuals producing theta locking in left-frontal electrodes (F3) indistinguishable from that of control subjects. Theta band activity appears highly malleable via

pharmacological intervention, as even a single five mg administration of melatonin can cause a significant increase in tonic theta band power (Cajochen et al., 1996).

As theta activity may arise from many different brain areas (Kahana, Sekuler, Caplan, Kirschen, & Madsen, 1999) and the functional role played by theta may vary with location (Ward, 2003), investigating specific topographical areas may prove beneficial in elucidating the purposes of this frequency band in both normal and pathological cognitive functioning. While primary sensory and motor areas are relatively spared by AD pathogenesis (Braak, Braak, & Bohl, 1993), hyperexcitability of motor (Ferreri et al., 2003) and visual sensory (Yener, Güntekin, Tülay, & Başar, 2009) cortical areas within the theta band have been documented. Peak theta amplitude and phase locking show the largest auditory and visual event-related decreases in AD in frontal-central regions during cognitive tasks (Yener, Güntekin, Öniz, & Başar, 2007; reviewed in Yener & Başar, 2013). Importantly, frontal sites also exhibit the most pronounced increases in theta power during active maintenance of information in WM tasks (Sauseng et al., 2004; Sauseng, Klimesch, Schabus, & Doppelmayr, 2005) in healthy subjects.

Some of the increased theta activity consistently found in resting state studies of AD is likely to be ‘slowed’ alpha activity (Klimesch, 1999; Steriade, Gloor, Llinas, da Silva, & Mesulam, 1990). Such slowing is typically observed in normal, as well as pathological, aging (Hartikainen, Soininen, Partanen, Helkala, & Riekkinen, 1992) and may be related to a decreased rate of cerebral blood flow to cortical grey matter (Stigsby, Jóhannesson, & Ingvar, 1981). Combined EEG and fMRI studies have shown

that an inverse relationship exists between the blood-oxygen-level-dependent (BOLD) signal and theta power (Michels et al., 2010; Scheeringa et al., 2009), and a negative correlation between hippocampal volume and theta power has also been noted (Grunwald, Hensel, Wolf, Weiss, & Gertz, 2007). Decreases in frequency may also signal deteriorating functional connectivity within cognitive networks, as better-connected feedback networks are assumed to produce higher frequency EEG readings (Klimesch, 1999). Lower frequency brain activity corresponds to larger neuronal areas contributing to the observed EEG signal, whereas higher frequencies indicate more spatially localized activity (Singer, 1993). Thus, the slowing observed in AD – and, to a lesser extent, regular aging – may also represent a mechanism by which the brain achieves the well documented compensatory activation (e.g. Grady et al., 2003; Sperling et al., 2003) patterns seen in neuroimaging studies of these groups.

Gamma. First observed in mammals following odorant stimulation of the olfactory bulb of the hedgehog (Adrian, 1942), gamma responses are also elicited by stimuli of sufficient magnitude arriving via all other sensory modalities. Following numerous early investigations linking gamma band activity (GBA) to sensory processes, GBA is now also associated with numerous higher order cognitive functions including selective attention, short- and long-term memory, and problem solving (Jensen, Kaiser, & Lachaux, 2007; reviewed in Rieder, Rahm, Williams, & Kaiser, 2011). Specifically, increases in gamma power have been shown to correlate with successful memory encoding (Long, Burke, & Kahana, 2014) and retrieval (Burke et al., 2014) in human subjects. In line with the distinction between SROs (early, phase-locked) and EROs (later, non-phase locked) previously mentioned, GBA can be roughly dichotomized into

sensory- and cognitive-related gamma (Başar, Başar-Eroğlu, Karakaş, & Schürmann, 1999). Sensory triggered GBA originates in cortical areas responsible for early stage processing of stimuli arriving via the corresponding sensory modality (Gruber, Trujillo-Barreto, Giabbiconi, Valdés-Sosa, & Müller, 2006; Herrmann, Fründ, & Lenz, 2010; Lachaux et al., 2000; Panteve et al., 1991), while cognitive-related GBA involves widespread activation of both cortical and subcortical areas (Başar, Schürmann, Başar-Eroglu, & Demiralp, 2001). Though there is evidence for overlapping functional correlates (Debener, Herrmann, Kranczioch, Gembris, & Engel, 2003; Engel, Fries, & Singer, 2001; Herrmann, Lenz, Junge, Busch, & Maess, 2004; Tiitinen et al., 1993) and neural origins (Basar, 1980; Herrmann, 2001; Pantev et al., 1991) of early and late GBA, the correspondence of early activity with sensory processes and later activity with cognitive operations generally holds (Karakaş, Başar-Eroğlu, Özesmi, Kafadar, & Erzengin, 2001).

Ascertaining the non-monolithic quality of the frequency band has done much to clarify the “gamma puzzle” (Karakaş & Başar, 1998) concerning the precise functional significance of GBA. Evidence suggests that the binding property of gamma oscillations facilitated by their high speed activity serves to tie together multi-modal sensory signals into singly experienced conscious percepts (Gray, 1994; Singer & Gray, 1995), while GBA simultaneously functions as a basic building block of electrical communication in the brain (Başar, Başar-Eroğlu, Karakaş, & Schürmann, 1999) as it performs many higher order cognitive functions. Early and late GBA are not wholly independent entities, however. Attention – perhaps the most often cited cognitive modulator of GBA (e.g. Debener, Herrmann, Kranczioch, Gembris, & Engel, 2003; Müller, Gruber, & Keil,

2000; Tiitinen et al., 1993) – has been shown to enhance early, sensory related GBA (but see Karakaş & Başar, 1998). This “spotlighting” effect of attention (Norman, 1968; Posner, 1980) thus provides evidence for top-down – in addition to bottom-up – mechanisms of stimulus processing in the brain and suggests that both may be subserved by GBA. The idea that all cognitive functions necessarily involve both memory and perception (Hayek, 1952; Fuster, 1997; Goldman-Rakic, 1996) further unites the two forms of GBA and underlies the match-and-utilization model (MUM) of Hermann and coworkers (2004). The MUM holds that memory matching is the primary cognitive functional correlate of GBA, underpinning all other gamma related cognitive processes. Furthermore, according to the MUM GBA may serve as an index of the strength of memory representations, as repeatedly associated objects strengthen synaptic connections between associated neurons leading to stronger oscillations in the gamma band for better remembered than for relatively novel stimuli.

The purported centrality of GBA to multiple higher cognitive functions has led to numerous investigations into the role activity in this frequency band may play in neuropsychiatric disorders such as AD. Given the strong evidential support for a correlation between GBA and cognitive functions in general and memory specifically, event-related testing paradigms focusing narrowly on this frequency band as an indicator of clinical cognitive impairment have thus far yielded somewhat underwhelming – and at times even contradictory – results. Several studies utilizing the resting state protocol have found the expected reduction in GBA among AD patients (König et al., 2005; Ribary et al., 1991; Stam et al., 2002), while others have failed to find significant reductions (Babiloni et al., 2004), or even found increased gamma band

power (van Deursen et al., 2008). Such discrepancies could be attributable to significant individual differences in GBA (Karakaş, Başar-Eroğlu, Özesmi, Kafadar, & Erzengin, 2001), methodological differences (van Deursen et al. 2008), and/or frequency-band specific effects of medication. To this last point, the significant loss of basal forebrain cholinergic neurons seen in AD (Coyle, Price, & Delong, 1983; Whitehouse et al., 1982) might be expected to significantly impact GBA, as acetylcholine has proven important to oscillatory synchronization in the gamma band (Rodriguez, Kallenbach, Singer, & Munk, 2004). Acetylcholinesterase inhibitors (AChEI), often prescribed for AD patients, have been shown to normalize the EEG of AD patients by reducing the typical slowing pattern seen in the disease in both short- (Adler & Brassen, 2001) and long-term (Jelic et al., 1998; Kogan et al, 2001) testing windows. Reduced GBA observed in normal ageing (Böttger, Herrmann, & von Cramon, 2002) may be attributable to age-related decreases in dopamine D2 receptors (Bäckman, Nyberg, Lindenberger, Li, & Farde, 2006; Li, Lindenberger, & Sikström, 2001), while the dopamine system is relatively spared by the pathogenic processes of AD (Rossor & Iversen,1986). Such results suggest that reduced GBA observed in normal ageing may be mediated by different neurotransmitters and neural networks than is the decrease wrought by AD pathogenesis.

Theta-gamma coupling. A fundamental feature of oscillatory activity in the brain is the modulation of localized, high speed activity by more widespread, low frequency rhythms (Bragin et al., 1995; Chrobak & Buzsáki, 1998; Lakatos et al., 2005). *Cross-frequency coupling* (CFC) - a statistical relationship between spectral elements of different frequency bands - reveals complex, non-linear interactions between neuronal

populations and can be observed both within and between brain regions (Onslow, Bogacz, & Jones, 2011). While CFC has been detected between different frequency band pairs and occurs in several brain regions including sensory (Lakatos et al., 2005) and frontal cortex (Canolty et al., 2006), the most studied example of CFC involves theta and gamma activity in the hippocampus (e.g. Axmacher et al., 2010; Buzsáki & Draguhn, 2004; Mormann et al., 2005). Attempts at direct, 1:1 mapping of frequency band activity in the brain onto particular behavioral and/or cognitive states has widely met with failure, as evidenced by the ever-evolving notions regarding the behavioral significance of theta band activity (Buzsáki, 2011) and the sensory versus cognitive debate described as the gamma paradox (Karakaş & Başar, 1998). As "the coupling of two or more oscillators could provide enhanced combinatorial opportunities for storing complex temporal patterns and optimizing synaptic weights" (Buzsáki & Draguhn, 2004, p.1929), investigations of CFC should greatly enhance the likelihood of elucidating behavioral and cognitive correlates of frequency band activity. Interactions between frequency bands revealed through CFC may, for instance, help explain the numerous contradictory findings regarding changes in specific frequency band power during successful memory encoding (reviewed in Hanslmayr & Staudigl, 2014).

As reviewed briefly in previous sections, activity in both theta and gamma bands is modulated during memory tasks. Activity within each frequency band is thought to both reflect and facilitate functional network connectivity, simultaneously allowing specialized neuronal assemblies to encode information independently and interact selectively according to situational demands (Fries, 2009; Varela, Lachaux, Rodriguez, & Martinerie, 2001). However, it is now believed that interaction between – as well as

within – individual frequency bands is required for the complexity required for higher cognitive functioning (Le Van Quyen, 2011). GBA is highly localized, yet the results of any local cortical computations must somehow be integrated globally (Buzsáki & Draguhn, 2004). When contributions from higher association areas are required for the execution of cognitive processes such as manipulating items in WM or consolidating memories via the hippocampus, slower frequencies such as theta are needed to link spatially localized GBA (Başar, Başar-Eroğlu, Karakaş, & Schürmann, 2000; Klimesch, 1999; Sirota et al., 2008).

Any pair of spectral properties (frequency, amplitude, phase) for a given signal can theoretically exhibit coupling behavior (Hyafil, Giraud, Fontolan, & Gutkin, 2015), but the most studied manifestations of CFC are phase-frequency, phase-phase (aka n:m phase synchronization), phase-amplitude, and amplitude-amplitude coupling (Hyafil, Giraud, Fontolan, & Gutkin, 2015; Jensen, & Colgin, 2007). Only phase-amplitude coupling (PAC) will be discussed further here, as mounting evidence suggests that theta-gamma PAC is important to memory processes (Axmacher et al., 2010; Friese et al., 2013; Fuentemilla, Penny, Cashdollar, Bunzeck, & Düzel, 2010; Heusser, Poeppel, Ezzyat, & Davachi, 2016; Lega, Burke, Jacobs, & Kahana, 2014). PAC – also called nested oscillation – represents the coupling of the phase of low frequency activity to the amplitude of faster activity (Heusser, Poeppel, Ezzyat, & Davachi, 2016), and has been proposed as a mechanism to explain phenomena such as working memory capacity (Lisman & Idiart, 1995) and the number of visual items that can be processed within a single perceptual ‘snapshot’ (VanRullen & Koch, 2003). In the case of working memory capacity, Miller’s (1956) famous “magical number seven

plus or minus two" corresponds to the approximately seven gamma cycles that can nest within a single cycle of theta.

Generally, PAC posits that individual items are represented by neural cell assemblies operating in high (i.e. gamma) frequency bands, and that these individual items – carried as gamma cycles – are ordered along the phase of an underlying slower rhythm (Lisman & Idiart, 1995). PAC has been proposed as a means of encoding the temporal order of episodic memories (Heusser, Poeppel, Ezzyat, & Davachi, 2016) and as a mechanism involved in learning specific associations between items by grouping them together in a compressed time window (Fell & Axmacher, 2011; Jensen, Idiart, & Lisman, 1996). Memory formation by grouping disparate features together via temporal association fits well with the temporal correlation hypothesis, which holds that the simultaneous firing of neurons indicates that they code features of the same object (Singer & Gray, 1995; Von Der Malsburg & Schneider, 1986).

Measuring CFC is a recently developed and rapidly burgeoning method of indexing brain functionality that has yet to be widely investigated in the context of clinical memory deficits as seen in MCI and AD: As such, no specific hypothesis is adopted here regarding differential theta-gamma coupling strength between these two populations. In line with the bulk of previous research, event-related power in both theta and gamma bands is expected to exhibit less increase over baseline in AD relative to MCI cases, with the AD group also expected to show diminished ITPC. Regarding expected power changes from baseline: Tonic theta frequency power, as previously discussed, is characteristically elevated in AD, which should correspond to a small or

even negative event-related power change – relative to this elevated baseline – in AD individuals relative to MCI individuals, if cognitive functions (especially memory performance) indexed by the oddball paradigm are significantly reduced in the former population. Despite the dearth of consistent empirical evidence demonstrating reduced gamma band frequency power in AD and/or MCI, more pronounced overall slowing of the EEG in AD combined with the generally accepted positive association between gamma band power and memory performance suggests that gamma band power should be anticipated to be lower in AD relative to MCI. ITPC, as an index of the consistency of signal phase over trials within each diagnostic condition, can be taken to reflect the uniformity of the timing of neural activity in response to incoming stimuli (Sauseng & Klimesch, 2008). As such, it is expected that individuals with AD will show reduced ITPC due both to attention deficits related to damaged cholinergic basal forebrain areas as well as to generally reduced neural network connectivity and functionality due to widespread synaptic loss and neuronal atrophy associated with advancing AD pathology.

Method

Participants

Data were obtained from 60 older adults recruited from an outpatient memory clinic. Participants were patients diagnosed with either aMCI (n = 29; M_{age}=73.0; SD_{age}=9.32) or probable AD (n = 31; M_{age}=78.29; SD_{age}=8.28) according to revised NIA-AA criteria (McKhann et al., 2011) pre-screened for negative history of other neurological conditions (e.g. stroke, seizure disorder, traumatic brain injury). All

participants received financial compensation for participation. Twelve participants (n_{MCI} = 1, n_{AD} = 11) were being treated with cholinesterase inhibitors (donepezil) at the time of participation, two participants with AD had also been prescribed the NMDA receptor antagonist memantine, and medication information was unavailable for 30 participants (n_{MCI} = 16, n_{AD} = 14). Four participants with incomplete data resulting from technical issues during data collection (n = 2) or requests to discontinue (n = 2) were excluded from analyses. Assent was obtained from each participant and written informed consent was obtained from a surrogate present at the time of participation, in compliance with institutional protocols.

Materials

All participants performed cognitive, hearing, and vision assessments prior to having their EEG data recorded while performing a computerized set of tasks designed to activate selected neurological processes.

Cognitive Assessment. The Montreal Cognitive Assessment (MoCA), a brief, comprehensive screening tool designed to be sensitive to early changes across major cognitive domains (Nasreddine et al., 2005), was used to assess global cognitive function. The MoCA is a 30-point screening tool with a clinical cutoff of 26 (scores less than 26 indicate possible cognitive impairment). Seven sub-scores can be calculated for items in visuospatial/executive, naming, attention, language/fluency, abstraction, delayed recall, and orientation domains.

Vision Assessment. Visual acuity at the time of testing was calculated with a standard Snellen chart.

Hearing Assessment. The Hearing Handicap Inventory for the Elderly-Screening Version (HHIE-S; Ventry & Weinstein, 1982), a 40-point, 10-item questionnaire, was given to assess individual perception of the social and emotional effects of hearing loss. Scores of 0-8 denote no self-perceived handicap; Scores of 8-22 suggest mild-moderate handicap; Scores of 24-40 indicate significant handicap.

Neurometric Assessment. Responses to visual oddball stimuli analyzed throughout this paper were collected as part of a brief neurometric battery (BNB; Kieffaber, Okhravi, Hershaw, & Cunningham, 2016) in which a series of non-overlapping auditory and visual stimuli are presented over a 2600 ms interval. This electrophysiological battery was programmed in MATLAB (R2012b; The Mathworks, Inc., Natick, MA). Task instructions were presented on-screen and reviewed verbally with the participant to ensure comfort with the requirements of the task. Three practice rounds, each consisting of 10 trials, were provided. The first practice round consisted solely of target stimuli; additional visual stimuli were added in the second practice round; and auditory stimuli were incorporated in the final practice sequence. The battery contained 400 total trials with a self-timed break provided after 200 trials.

Visual stimuli. Visual stimuli were presented on a computer monitor against a gray background. In each trial, a number (‘1’ or ‘2’) and letter (‘X’ or ‘O’) were presented laterally with respect to a continuously-displayed central fixation, subtending a visual angle of 14.25°. The design was counterbalanced such that 50% of participants were directed to respond to letters, and 50% were directed to respond to numbers. Participants were instructed to attend to either numbers or letters (e.g. “Press the left

control button if you see a ‘1’ and the right control button if you see a ‘2’”), with responses entered on a standard QWERTY keyboard. For each participant, stimuli in the target set were randomly assigned to be either standard or deviant (oddball). Oddball targets were presented on 15% of trials, enabling measurement of an oddball ERSP. Visual stimuli were presented for a fixed duration of 250 ms, with variable onset in the interval 200-1050 ms from the start of a trial.

Procedure

Participants were invited to take part in the study following a scheduled visit to their regular outpatient memory clinic. After participants and surrogates provided assent and informed consent, respectively, participants were administered the MoCA, hearing, and vision assessments. Following these assessments, participants were fitted with an EEG cap and completed the neurometric battery. From consent to completion, the procedure lasted approximately one hour.

EEG recording and analysis. Continuous electrophysiological data were recorded using a high-impedance DBPA-1 Sensorium bio-amplifier (Sensorium, Inc., Charlotte, VT) with an analog high-pass filter of 0.01 Hz. Recordings were acquired at a rate of 2000 samples per second from an extended 10/20 cap system with 21 Ag-AgCl sintered electrodes while participants were seated facing a computer monitor in an unshielded, unlit room. The ground electrode was positioned on the center of the forehead and the reference was affixed to the right side of the nose. Impedances were adjusted to be within 0-20 kΩ prior to each recording session.

EEG data were processed offline in MATLAB R2016a (The Mathworks, Inc., Natick, MA) using the EEGLAB (Delorme & Makeig, 2004) toolbox. Raw data were resampled to 1000 Hz and an initial IIR Butterworth 0.1-100 Hz band-pass filter was applied (half-amplitude cutoff of 6 dB, roll-off of 12 dB/octave). Data were visually inspected, and channels containing extreme artifact were interpolated. A maximum of five channels were interpolated for any participant (*M* = 1.06, *SD* = 1.62). Ocular artifacts were identified and removed using the ***runica*** EEGlab toolbox function, which utilizes an infomax independent component analysis (ICA) algorithm (Delorme & Makeig, 2004; Jung et al., 2000). After pre-processing to remove extreme artifact, each channel of EEG data was decomposed into the five classically defined EEG sub-bands: delta (0.5–4 Hz), theta (4–7 Hz), alpha (8–12 Hz), beta (13–30 Hz) and gamma (30–40 Hz).

Frequency, time-frequency, and ITPC measures. Continuous EEG was decomposed using the EEGlab toolbox functions ***spectopo*** (frequency power) and ***newtimef*** (time-frequency power and ITPC)***.*** Both functions measure the power and/or phase consistency of the underlying signal by means of complex Morlet wavelet transformation, which provides a good compromise between time and frequency resolution (Sinkkonen, Tiitinen, & Näätänen, 1995). Analyses utilized a 200 ms pre-stimulus baseline period along with all ***newtimef*** default wavelet parameters.

Phase-amplitude coupling measure. Strength of theta-gamma coupling was measured with the modulation index (MI; Canolty et al., 2006) as implemented in the freely available MATLAB code developed by Onslow and colleagues (2011). In this

particular implementation, instantaneous amplitude and phase are first calculated over the range of frequencies contained in the signal by filtering the continuous EEG data via convolution with complex Morlet wavelets, with instantaneous amplitude given by the absolute vale of the analytic signal and instantaneous phase given by the phase angle of the complex-valued signal (Onslow, Bogacz, & Jones, 2011). The MI measure generates a joint probability density function in the complex plane arising from the composite of the envelope values of the amplitude of the higher frequency signal and the instantaneous phase of the lower frequency signal, with non-zero MI values indicating that particular amplitude and phase values tend to co-occur in time (Onslow, Bogacz, & Jones, 2011).

Statistical Analysis

Participant-level characteristics (see Table 1) were tested for group differences with independent-samples *t*-tests. ERSP, ITPC, and PAC measures at electrode locations Fz, Cz, Pz, and Oz were compared. ERSP and event-related ITPC values for standard stimuli were first subtracted from values of oddball trials to derive a measure of the oddball effect for the AD and MCI groups individually (see Figures 2 & 3). This level of subtraction provides a measure of the cognitive processes involved in detecting and selecting target stimuli removed from the sensory related spectral activity involved in simply viewing standard stimuli. Group level oddball effects were then subject to another round of subtraction (MCI – AD; see Figures 4 & 5) in order to compare the differences in the spectral values associated with the cognitive processes involved in the oddball paradigm between the two groups at each time point in the analysis. MI

values of PAC between theta (4-8 Hz) and a range of gamma frequencies spanning from 33-83 Hz in steps of 5 Hz were compared between the two groups. As all ERSP, ITPC, and PAC analyses were performed at each electrode location across multiple frequency bands, with ERSP and ITPC analyses additionally performed at each time point, *p*-values (when initially significant) were adjusted for multiple comparisons using the false discovery rate (FDR) method of Benjamini and Hochberg (1995).

Results

For ERSP and ITPC comparisons, timepoints after approximately 300 ms (taken to reflect cognitive, rather than sensory processing) were examined.

Comparing differences in oddball effect elicited ERSP between groups (see Figure 4) did not indicate significant differences within the gamma or theta bands of interest at any electrode location. Highly similar oddball event related frequency band power responses are also seen at all electrode locations and all frequency bands when averaging activity over time (see Figure 1).

Comparing differences in oddball effect elicited ITPC between groups (see Figure 5) revealed a consistent pattern at all central electrode locations of significant differences within the gamma band focused around 30-40 Hz within a time range of 300-500 ms post-stimulus. Somewhat counterintuitively, ITPC values for AD were higher than those for MCI (see Discussion section).

Comparing differences in oddball effect elicited PAC between groups did not indicate significantly different theta-gamma coupling at any electrode location. PAC values did not correlate strongly with either MoCA scores or hippocampal occupancy

measures (see Table 2) commonly used in the diagnosis of AD. Ignoring diagnostic group, standard and oddball visual stimuli did not elicit significantly differing PAC MI values ($t(59) = -1.80 – 1.76$, $p = 0.08 – 0.97$, *ns*; see Discussion section). There was also no interaction between diagnostic condition and stimulus type ($t(1)=0.54$, $p=0.46$, *ns*).

Discussion

Overall, ERSP and PAC measures failed to show distinctive differences between AD and MCI groups, while ITPC exhibited significant differences within the time range of interest in an unexpected direction (higher in AD). The pattern of results observed in this study is consistent with oft-conflicting results of EEG-derived indices of AD and/or MCI reported in the extant literature and, perhaps, reflective of highly variable underlying patterns of neural pathology presented by such clinically heterogeneous diseases.

Visual inspection of oddball effect ERSP plots (see Figure 4) shows a consistent, rhythmic pattern of gamma power increases in both patient groups beginning at ~100 ms post-stimulus and continuing throughout the remainder of these epochs. One can imagine a sinusoidal wave at theta frequency snaking through these clusters of high gamma activity, suggesting that activity in the ~30 – 50 Hz range is being modulated at theta frequency during oddball trials, even if this modulation does not differ to a statistically significant extent between diagnostic categories. These islands of high gamma power occur much more regularly in MCI patients, with the clusters of gamma

also taking place at higher frequency and are confined to a tighter frequency range for MCI as compared to AD individuals (~ 45-50 Hz for MCI vs. ~30-40 Hz for AD).

Higher gamma ITPC values observed in AD relative to MCI cases could be explained by a non-linear, U-shaped pattern of disease-related change in this metric as individuals advance from MCI to AD. ITPC increases at 400ms between 30-40 Hz (see Figure 5) seen at all three electrode locations could also be indicative of additional, compensatory neural activation triggered within the brains of AD patients in order to attend to and recognize oddball stimuli. A third possibility is that a much higher proportion of AD participants were taking prescription AChEI (see Limitations section) and the observed higher gamma ITPC in this group could be a pure medication effect. As it has been observed (Başar, 2013) that medication status can drastically alter the electrical signals observed and thus the overall picture of cognitive functioning and how it relates to disease pathology in any study investigating cognitive impairment utilizing frequency domain analysis, results observed here must be interpreted with caution.

While PAC values did not reliably differentiate between the AD and MCI groups of our sample, the fact that PAC values for standard and oddball visual stimuli did not differ significantly even within subjects suggests that other paradigms (or a different implementation of the oddball paradigm) may provide a better measure of cognitive event related PAC. Also, there are many quantification methods in addition to the MI used to measure PAC here (Canolty et al., 2006; Onslow, Bogacz, & Jones, 2011), and perhaps future investigations will find that a different calculation method possesses more desirable statistical properties for applications such as this.

Conclusions

To advance the development of treatment interventions to prevent, or at least to delay, the onset of the debilitating behavioral and cognitive impairments brought on by AD, practical and cost effective tools that can help to both identify at-risk individuals at the earliest possible juncture and to quantifiably assess disease progression are urgently needed. Criteria for an ideal biomarker of AD developed by the Ronald and Nancy Reagan Research Institute of the Alzheimer's Association and the National Institute of Aging Working Group (Davies et al., 1998) state that such a marker should be: reliable, non-invasive, simple to perform, precise, inexpensive, and able to detect a fundamental feature of AD neuropathology. The ability to monitor brain activity with the millisecond temporal resolution required to gauge neuronal synchrony and measure the integrity of synaptic transmission, along with cost and ease of use advantages relative to other neuroimaging methods and molecular chemical assays, all recommend electroencephalograph (EEG) recordings as an informative and practical diagnostic tool in the battle against AD.

While the idea of a rhythm disease is not new (Buzsáki, 2011; John, 1977), developing consensus that oscillatory activity detectable via EEG plays a functional role in neuronal communication has only recently led some to consider AD within this category (Nimmrich, Draguhn, & Axmacher, 2015). Viewing a neurological and psychiatric disorder such as AD as a dysrhythmia or oscillopathy provides a fresh perspective that might yield new insights into the condition (Palop, Chin, & Mucke,

2006) at a time when the prevailing amyloid cascade hypothesis appears increasingly untenable (Herrup, 2015).

This paper briefly summarized previous work in both clinical and basic research domains pertaining to memory related ERSP, ITPC, and CFC activity in/between the theta and gamma frequency bands. Results from the visual oddball task presented here suggest that gamma band ITPC exhibits significant differences between AD and MCI groups within a time window of ~300-500 ms, indicating that this measure merits further investigative attention in the context of discriminating between cases of AD and MCI.

Limitations

Medication information was only available for half of our sample population, precluding comparisons between medicated and *de novo* conditions. While effects of AChEI upon individual frequency band power and phase locking have been well documented, little is known as to how this medication may impact interactions between frequency bands such as CFC. Comparing MI values of PAC for the portion of our sample with medication information showed a non-significant between group difference.

This study included no dedicated control group, preventing direct comparison between healthy and pathological groups using the measures derived herein. While the main thrust of this research was to uncover EEG derived indicators that may be useful in distinguishing AD from MCI, including an age-matched control group would provide a better picture of the overall spectrum of functional impairment changes in these measures may represent.

Some authors (e.g. Donner & Siegel, 2011; Klimesch, 1999) have recommended eschewing classical frequency band definitions, advocating that data-driven frequency grouping done at the individual participant level better capture oscillatory dynamics that may take place over multiple or be limited to only a portion of traditional frequency ranges. In the opinion of this author, such an approach would make for highly circular inferences while severely limiting both the generalizability of findings and the ability to compare results to those of previous studies: Thus, classic frequency bands were examined.

Commonly implemented calculations of CFC, including the measure of PAC used herein, yield poor temporal resolution (Tort, Komorowski, Eichenbaum, & Kopell, 2010), negating the main advantage EEG/MEG holds over other neuroimaging methods. Additionally, longer trial epochs than were used in the current study would have proven beneficial in resolving low-frequency signal characteristics.

Directions for Future Studies

Event-related PAC (ERPAC; Voytek, D'Esposito, Crone, & Knight, 2013) analysis would help to address the issue of poor temporal resolution and could yield important insights into the time course of PAC and how this metric may differ between AD and MCI populations.

Source localization of all signals of interest would help to better pinpoint and differentiate the contributions of specific neuronal assemblies to the observed EEG indicators and could facilitate better targeted treatment interventions. Additionally, performing source localization of theta and gamma activity separately as well as for the

coupled theta-gamma PAC value could indicate when and where these signals are most prevalent individually while performing oddball-type visual discrimination tasks as well as where they most strongly interact.

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Table 1

Participant Characteristics by Diagnostic Category

	aMCI (*n* = 29)	AD (*n* = 31)	
	M (*SD*)	*M* (*SD*)	*t(df)*
Age (years)	73.00 (9.32)	78.29 (8.28)	-2.32(58)*
Education (years)	15.24 (2.28)	13.89 (2.30)	2.22(55)*
Gender (*n* female)	17	22	
MoCA (__/30)	21.34 (2.41)	16.74 (4.20)	5.16(58)**
Vision (20/__)	30.69 (11.24)	31.00 (9.51)	-0.12(57)
Hippocampal Volume (cm^3)	6.67 (1.11)	6.08 (0.98)	1.84(41)
Inferior Lateral Ventricle Volume (cm^3)	2.79 (1.33)	3.62 (1.69)	-1.79(41)
Lateral Ventricle Volume (cm^3)	38.99 (15.90)	52.94 (30.94)	-1.90(41)
Hippocampal Occupancy score	0.71 (0.11)	0.64 (0.11)	2.12(42)*

Notes. * $p < .05$; ** $p < .01$. Hippocampal occupancy score is calculated as the ratio of hippocampal volume to the sum of hippocampal volume and inferior lateral ventricle volume.

Table 2

Correlations Among Key Participant Variables and PAC Values

Variables	HipOc	Age	MoCA	Educ.	Vision	PACfz	PACcz	PACoz
HipOc.		-.49**	.28	.22	.03	-.05	.02	-.11
Age			-.31*	-.32*	.25	-.04	-.01	.20
MoCA				.29*	-.05	.12	.07	.09
Educ.					-.02	.35**	.41**	.16
Vision						-.01	-.02	.07
PACfz							.80**	.42**
PACcz								.53**
PACoz								

*Notes. * p < .05; ** p < .01.* PAC values at locations Fz, Cz, and Oz were log transformed prior to correlation. HipOc. = hippocampal occupancy score. Educ. = years of education.

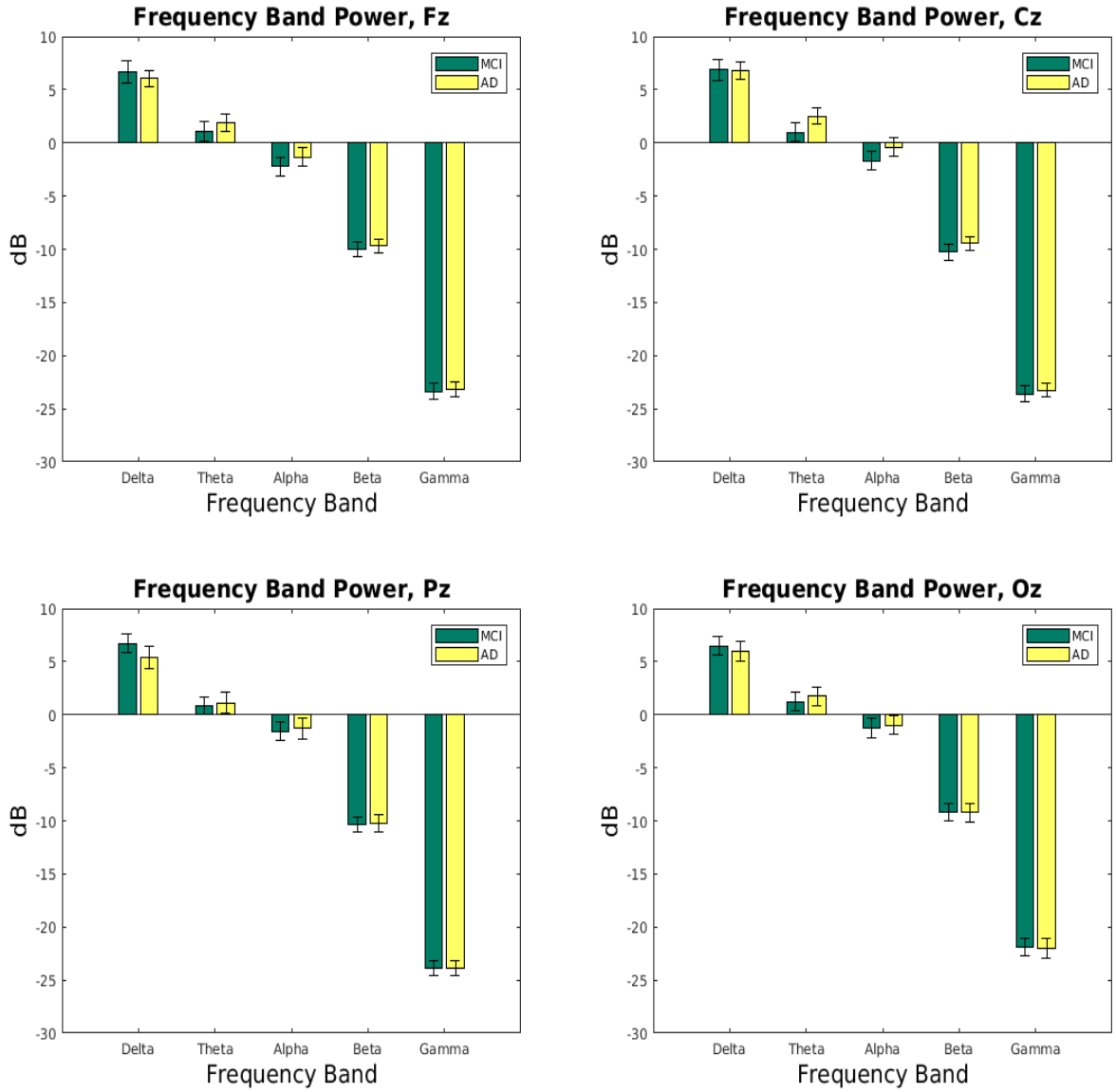
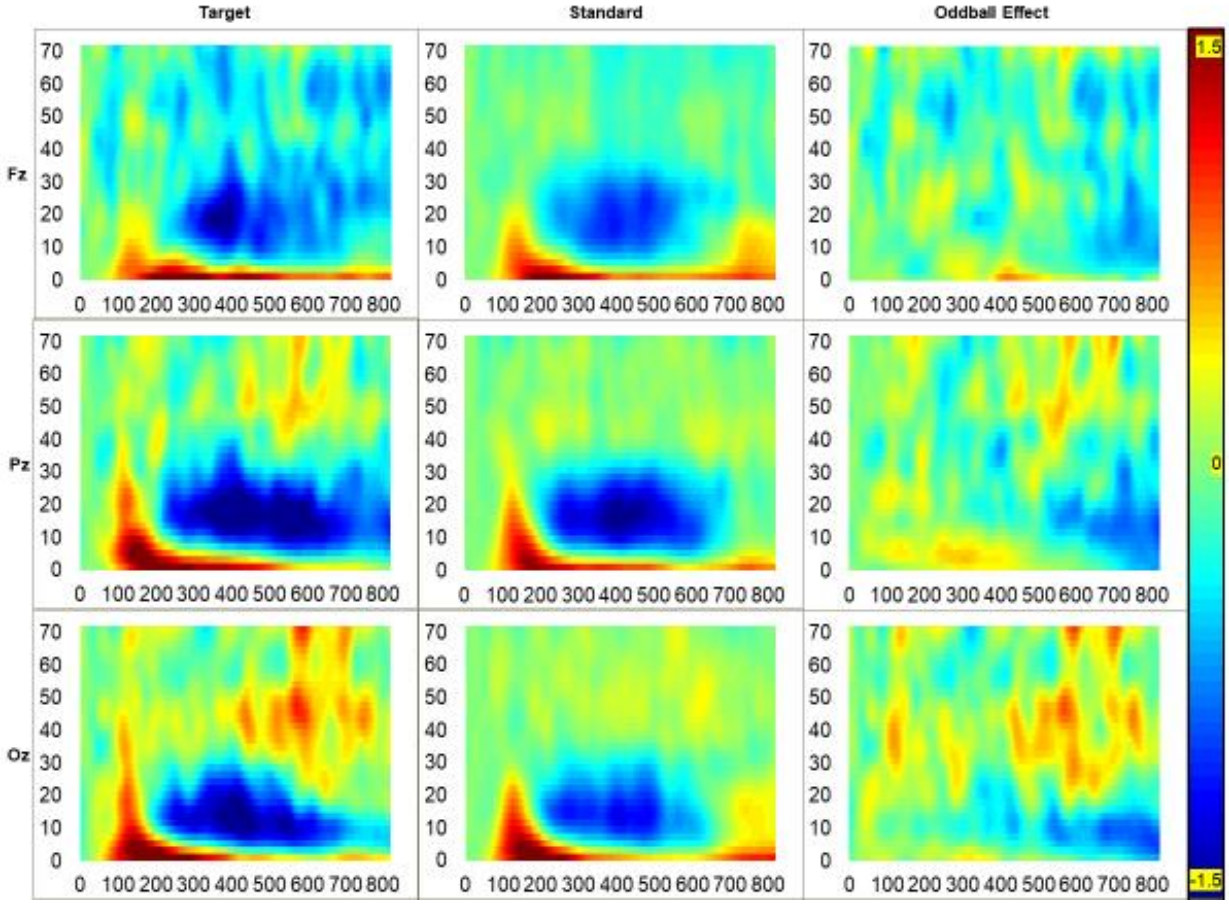
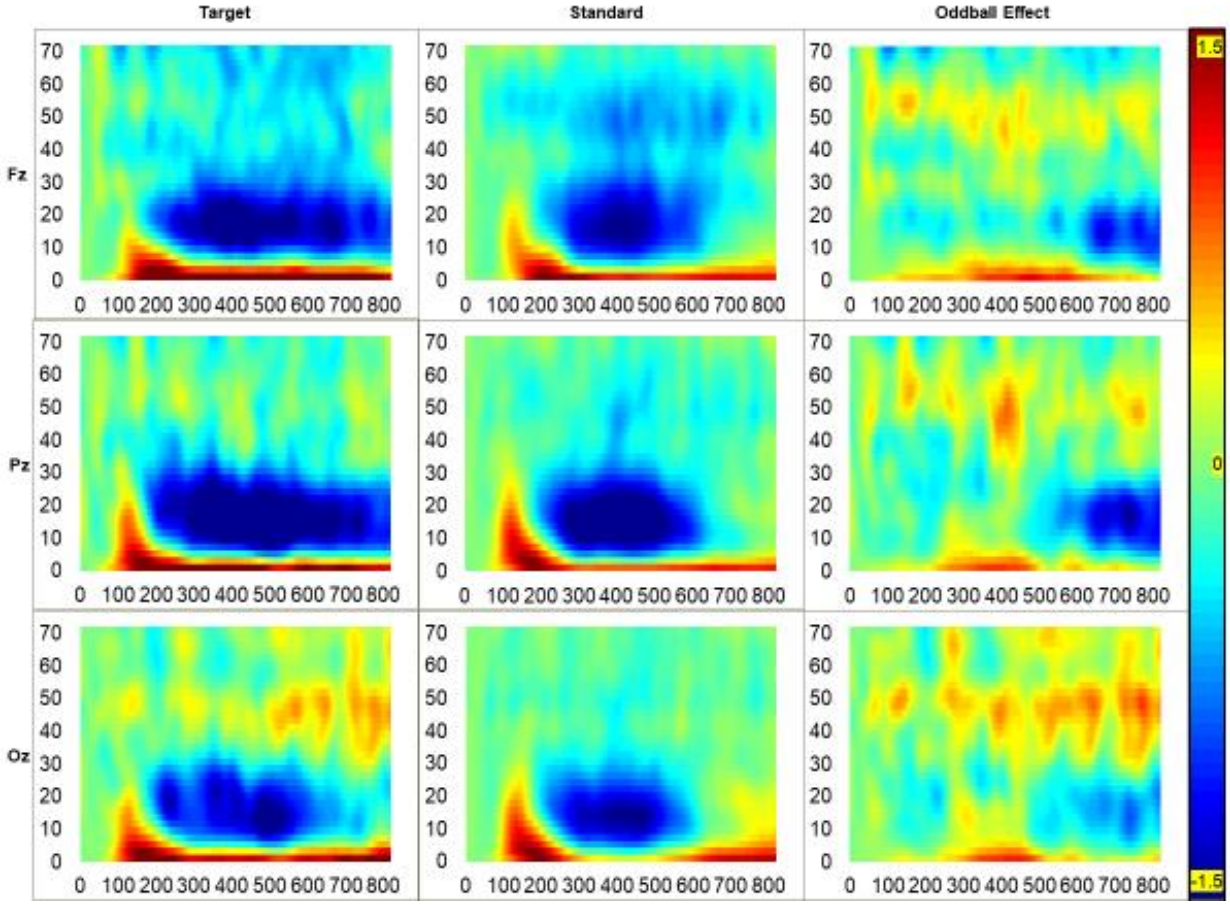


Figure 1. Event related frequency band power by diagnosis for oddball trials at hemispheric midline electrode locations, ordered (from the front of the head to the back) Fz, Cz, Pz, Oz. All between-group differences statistically non-significant ($p > 0.05$). Bars indicate the standard error of the mean.



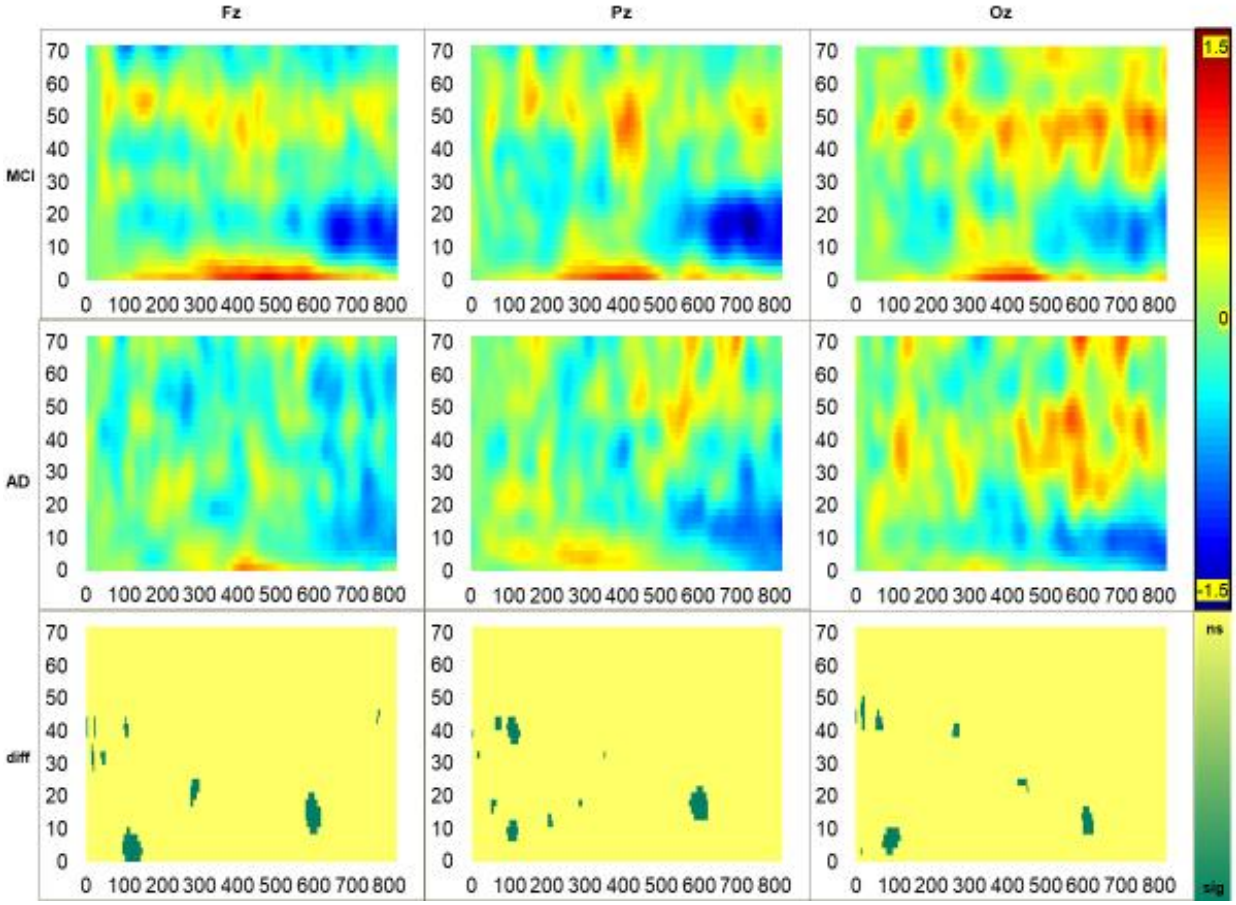
X axis = Time in milliseconds
Y axis = Frequency in hertz
Z axis = dB normalized power change from baseline

Figure 2. Deriving oddball-effect (Target – Standard visual stimuli) ERSP plots for AD participants.



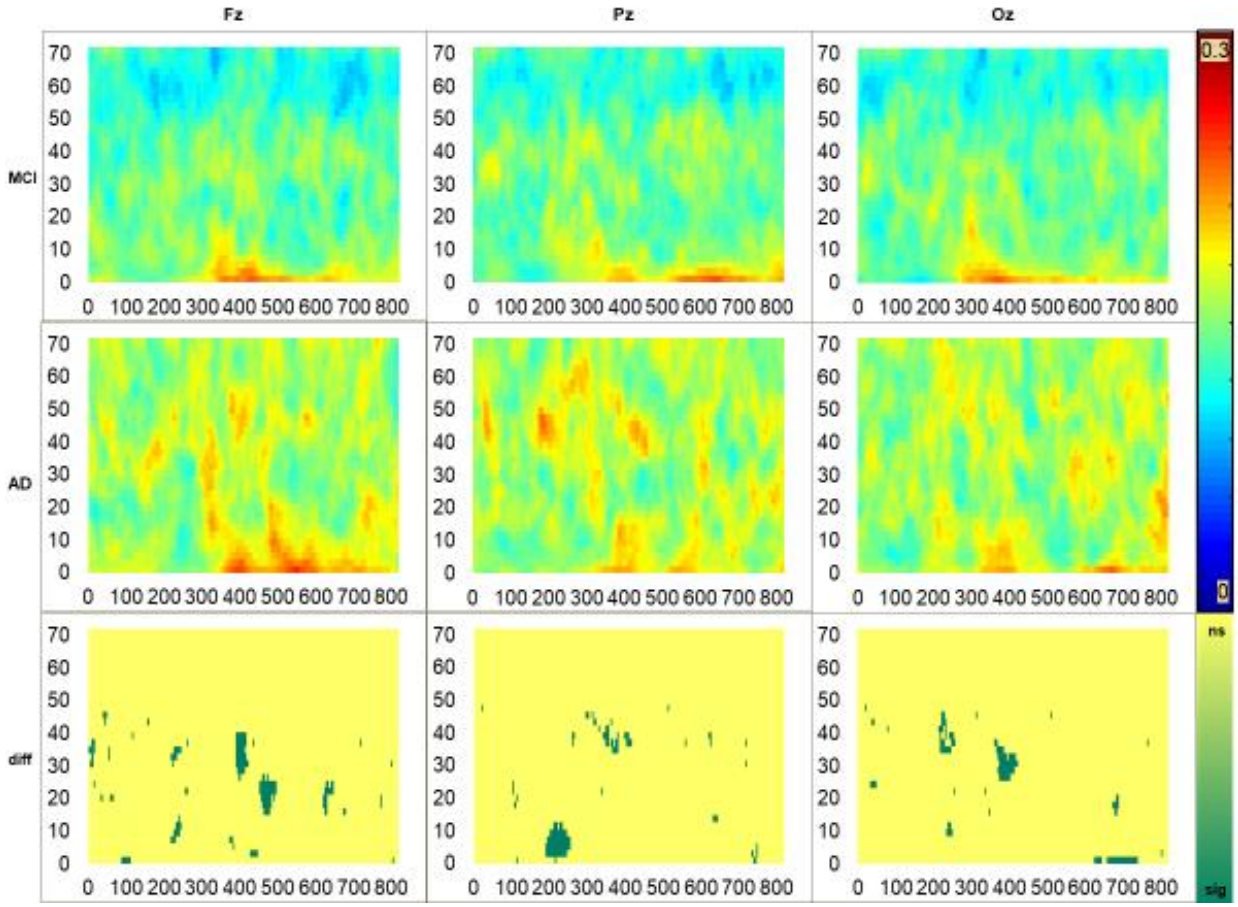
X axis = Time in milliseconds
Y axis = Frequency in hertz
Z axis = dB normalized power change from baseline

Figure 3. Deriving oddball-effect (Target – Standard visual stimuli) ERSP plots for MCI participants.



X axis = Time in milliseconds
Y axis = Frequency in hertz
Z axis = dB normalized power change from baseline or statistical significance

Figure 4. Comparing oddball-effect ERSP plots for MCI and AD participants. Significant differences shown in green indicate FDR-adjusted p <.05.



X axis = Time in milliseconds
Y axis = Frequency in hertz
Z axis = Phase Locking Value (range 0-1) or statistical significance

Figure 5. Comparing oddball-effect ITPC plots for MCI and AD participants. Significant differences shown in green indicate FDR-adjusted p <.05.