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From lab to clinic: the practicality of using event related potentials in the diagnosis of Alzheimer's disease

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Thesis

FROM LAB TO CLINIC: THE PRACTICALITY OF USING EVENT RELATED POTENTIALS IN THE DIAGNOSIS OF ALZHEIMER'S DISEASE

by

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CHEONGMIN SUH

ABSTRACT

The main objective of this study was to investigate whether event related potentials (ERPs) can be used as a biomarker of disease severity staging in Alzheimer's disease (AD) within a heterogeneous group of patients presenting to a memory disorders clinic for initial evaluation. Based on the known progression of AD pathology, we hypothesized ERP components would be abnormal, commensurate with disease severity in mild cognitive impairment (MCI) due to AD, mild, and moderate to severe dementia due to AD. ERP components were predicted based on the known sites of their neural generators. ERP peaks measured during an auditory oddball paradigm from twenty-two AD (n=9) and non-AD (n=13) patients were compared to their clinical outcomes using multivariate ANCOVA controlling for age with Bonferroni corrections. The predictive abilities of significant ERP components were examined using a binary logistic regression model. Significant between-group effects were found in N100 distractor amplitude, $F(2, 12) = 6.062$, $p = .015$, $\eta_p^2 = .503$. The results supported our hypothesis that N100 amplitude would be increased in AD, suggesting that sensory gating may be more impaired in mild AD than in non-AD related cognitive impairment.

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LIST OF ABBREVIATIONS

Aβ.....Amyloid beta

AD..... Alzheimer's Disease

ADC ..... Alzheimer's Disease Centers

BCa .....Bias Corrected Accelerated

BNT..... Boston Naming Test

BPA.....Button Press Accuracy

BU ..... Boston University

CA ..... *Cornu Ammonis*

CERAD .....Consortium to Establish a Registry for Alzheimer's disease

EEG.....Electroencephalography

EPSP ..... Excitatory Post-Synaptic Potential

ERP .....Event Related Potential

FA .....False Alarm

FAS .....Letter fluency task for letters F, A, and S

fMRI.....functional Magnetic Resonance Imaging

IPSP..... Inhibitory Post-Synaptic Potential

LC ..... Locus coeruleus

MCI..... Mild Cognitive Impairment

MMSE.....Mini-Mental State Examination

MoCA ..... Montreal Cognitive Assessment

MTL ..... Medial Temporal Lobe

NE ..... Norepinephrine

NFT .....Neurofibrillary Tangles

NIA ..... National Institute of Aging

NP .....Neuropsychological (tests)

PCA.....Posterior Cortical Atrophy

PFC .....Prefrontal Cortex

PiB-PET .....Pittsburgh Compound B Positron Emission Tomography

RT .....Reaction Time

SD .....Standard Deviation

TMT ..... Trail Making Test

VA.....Veterans Affairs

INTRODUCTION

1.1 Alzheimer's disease clinical features

Alzheimer's disease (AD) is a neurodegenerative disorder that begins insidiously with subtle changes, typically involving memory first, and then progressing to affect all cognitive domains. As this is a progressive disease, clinicians generally agree upon four broad stages of AD: mild cognitive impairment (MCI) due to AD, mild, moderate, and severe AD dementia (Budson and Solomon, 2016). Each stage is characterized by structural changes of the brain which result in deterioration of behavioral and cognitive function. Although impaired episodic memory is a hallmark of the disease, other cognitive domains deteriorate, including executive function (Tabert, Manly, Liu et al., 2006; Price et al., 1993), followed by semantic memory (Price et al., 1993), personality, and visuospatial abilities. Eventually, the loss of all cognitive abilities during the end stage of AD results in the need for constant care (Budson & Solomon, 2016). The behavioral hallmarks of deteriorating cognitive impairment, observed at each stage of the disease are summarized in table 1.

This project investigated the use of event related potentials (ERPs) as a candidate biomarker of disease severity staging in AD. ERPs are a cognitive measure that reflect synaptic changes in the brain and have been previously studied in the diagnosis of AD. The main objective of this study is to investigate whether ERPs can differentiate AD from non-AD related cognitive impairment, and can distinguish among the stages of clinical severity in AD. Given that AD typically progresses in a pathologically and neuropsychologically predictable manner, and that ERPs measure cognition based on the

physiological function of the brain, we anticipate that ERP measures will correlate with the degree of clinical severity. To our knowledge, this is the first study of its kind to implement ERPs as part of routine clinical workup in a memory disorders clinic, and to examine the sensitivity of ERPs to detect clinical severity.

Table 1. Behavioral and cognitive symptoms of MCI and stages of dementia due to AD.[1]

MCI due to AD	Mild dementia due to AD	Moderate dementia due to AD	Severe dementia due to AD
Very mild cognitive decline Slight memory lapses Poor word-finding Decline in ability to plan and organize	Memory loss Confusion about location or familiar places Taking longer to accomplish normal daily tasks Trouble handling money and paying bills Poor judgment leading to bad decisions Loss of spontaneity and sense of initiative Mood and personality changes, increased anxiety	Increasing memory loss Confusion Problems recognizing friends and family Poor judgment leading to bad decisions Difficulty organizing thoughts and thinking logically Inability to learn new things or to cope with new or unexpected situations Restlessness, agitation, anxiety, tearfulness, wandering Repetitive statements or movement	Inability to recognize family or to communicate Lost sense of self Weight loss Groaning, moaning, grunting Increased sleeping Lack of bladder and bowel control Seizures, skin infections, difficulty swallowing Aspiration pneumonia Death

[1] Adapted from Budson, A. E., & Solomon, P. R. (2016). Alzheimer's Disease Dementia and Mild Cognitive Impairment due to Alzheimer's Disease. *Memory Loss: A Practical Guide for Clinicians.*

		Hallucinations, delusions, suspiciousness, paranoia	

1.2 Neuropathology of AD

AD disrupts specific brain structures at each stage of the disease, as evidenced by post-mortem histopathological examination of AD brains. AD pathology typically starts in the entorhinal cortex of the medial temporal lobe (MTL) and then spreads quickly to the hippocampal formation, typically seen in MCI due to AD (Braak & Thal, 2011; Jack et al., 2000). In mild AD, AD pathology extends to the neocortical association areas which include the prefrontal, anterior superior temporal, and inferior parietal cortices, with association fibers in the cingulum bundle (Nieuwenhuys, 2008). In moderate to severe stages of disease, AD pathology affects virtually all parts of the brain including primary sensory centers of the neocortex (Braak & Thal, 2011) (figure 1).

The histopathological changes in AD brains have been corroborated by further studies using neuroimaging methods. For example, Whitwell and colleagues (2001), using functional magnetic resonance imaging (fMRI), correlated patterns of brain atrophy with histological pattern of AD pathology. Murray and colleagues (2015) used Pittsburg-compound B positron emission tomography (PiB-PET) to correlate PiB retention, which reflects burden of AD pathology, with AD clinical severity.

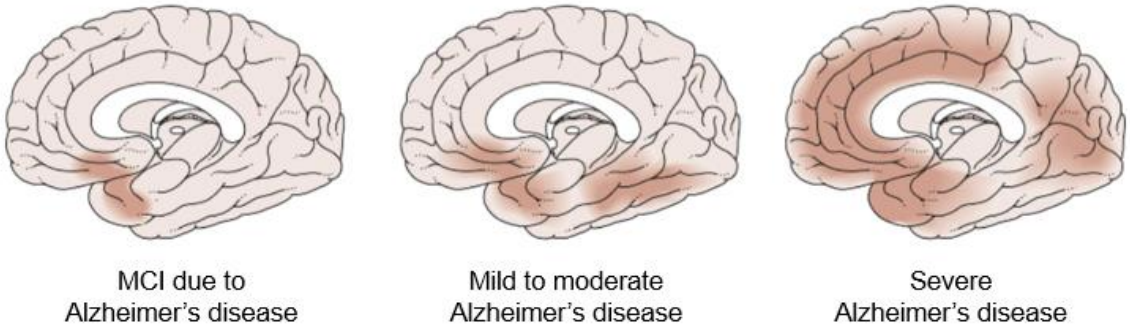

Figure 1. Spread of AD pathology in the brain at the different stages of Alzheimer's disease.[2]

Although the underlying pathophysiologic mechanism of AD is not yet fully understood, current research supporting the amyloid theory of disease propagation, suggests that the accumulation of tau neurofibrillary tangles (NFT) and amyloid beta (Aβ) results in synaptic loss and neurodegeneration (Raskin, Cummings, Hardy, Schuh & Dean, 2015; Selkoe & Hardy, 2016). Tau is a microtubule-associated protein that constitutes the neuronal cytoskeleton and provides structure to the cell. NFTs are abnormal, hyperphosphorylated tau proteins that remain after neuronal death. The presence of NFTs is more closely correlated with dementia severity in AD than is the accumulation of amyloid protein (Wilock & Esiri, 1982). Aβ is a 40- or 42-amino acid peptide segment of a larger, transmembrane glycoprotein known as the amyloid precursor protein. The accumulation of Aβ is thought to trigger subsequent pathophysiological damage which includes oxidative injury, activation of microglial and astrocytic inflammatory response, and hyperphosphorylation of tau protein, ultimately leading to

[2] Adapted from Budson, A. E., & Solomon, P. R. (2016). Evaluating the behavioral and psychological symptoms of dementia. *Memory Loss, Alzheimer's Disease, and Dementia: A Practical Guide for Clinicians. 2nd ed. Philadelphia, PA: Elsevier*.

neurofibrillary tangles (for review, see Raskin et al, 2015). This cascade is thought to result in widespread synaptic dysfunction and neuronal loss that manifest in the clinical hallmarks of AD (Jack et al., 2013; Raskin et al., 2015; Selkoe & Hardy, 2016). Additionally, it is hypothesized that beta-amyloid and NFT accumulate in the most vulnerable regions of the brain first, then spread by way of direct neuronal connections from one affected region to the next (Thal, Rub, Orantes & Braak, 2002).

NFT and Aβ pathology increases in both distribution and density as AD progresses, ultimately resulting in the gross anatomical changes and atrophy of specific brain structures seen in AD (Braak & Thal, 2011) (figure 2). In MCI due to AD, NFTs are predominantly observed in the MTL, specifically in the hippocampal formation, entorhinal and transentorhinal region, with involvement of subcortical structures such as the locus coeruleus (Braak, Alafuzoff, Arzberger, Kretschmar & Del, 2006). During this early disease stage, Aβ is often highly variable in spatial distribution throughout the brain. In some MCI patients, amyloid is entirely absent in the neocortex and in other cases, amyloid is present throughout both the neocortex and the medial temporal lobes (specifically, the CA1 field of the hippocampal formation and the entorhinal region), or even extends to include parts of the limbic lobe and subcortical structures such as the thalamus, hypothalamus and basal forebrain nuclei (Thal et al., 2002).

In mild AD dementia, additional NFTs are observed in the neocortex of the fusiform and lingual gyri and the CA3 and CA4 regions of the hippocampus (Braak et al., 2011). The locus coeruleus, the transentorhinal and entorhinal regions and CA1 and CA2 of the hippocampus, all of which often contain NFTs beginning in MCI, show greater

density of tangles in mild AD. As mild AD worsens, NFT accumulation extends into the subiculum of the hippocampal formation and the neocortical association areas. As in MCI due to AD, Aβ may be observed again in spatially variable patterns of distribution during mild AD. In some cases of mild AD, amyloid is entirely absent in the neocortex and in other cases, plaques may be seen in the neocortex and extending into the subcortical structures including the central gray nucleus, superior colliculus, red nucleus, inferior olivary nucleus and the substantia nigra (Thal et al., 2002).

During moderate to severe stages of AD, additional NFTs are found in the secondary and primary neocortical areas of the frontal, temporal and parietal lobes and extends into the peristriate and striate regions of the occipital cortex (Braak et al., 2011). Regions that had been affected by NFT accumulation in prior AD stages, now show increased density of NFTs. Aβ is observed in the regions mentioned in the MCI and mild AD stages, along with possible extension into the pons and its nuclei, central and dorsal raphe nuclei, locus coeruleus, parabrachial nuclei, dorsal tegmental nucleus, and the cerebellum (Thal et al., 2002).

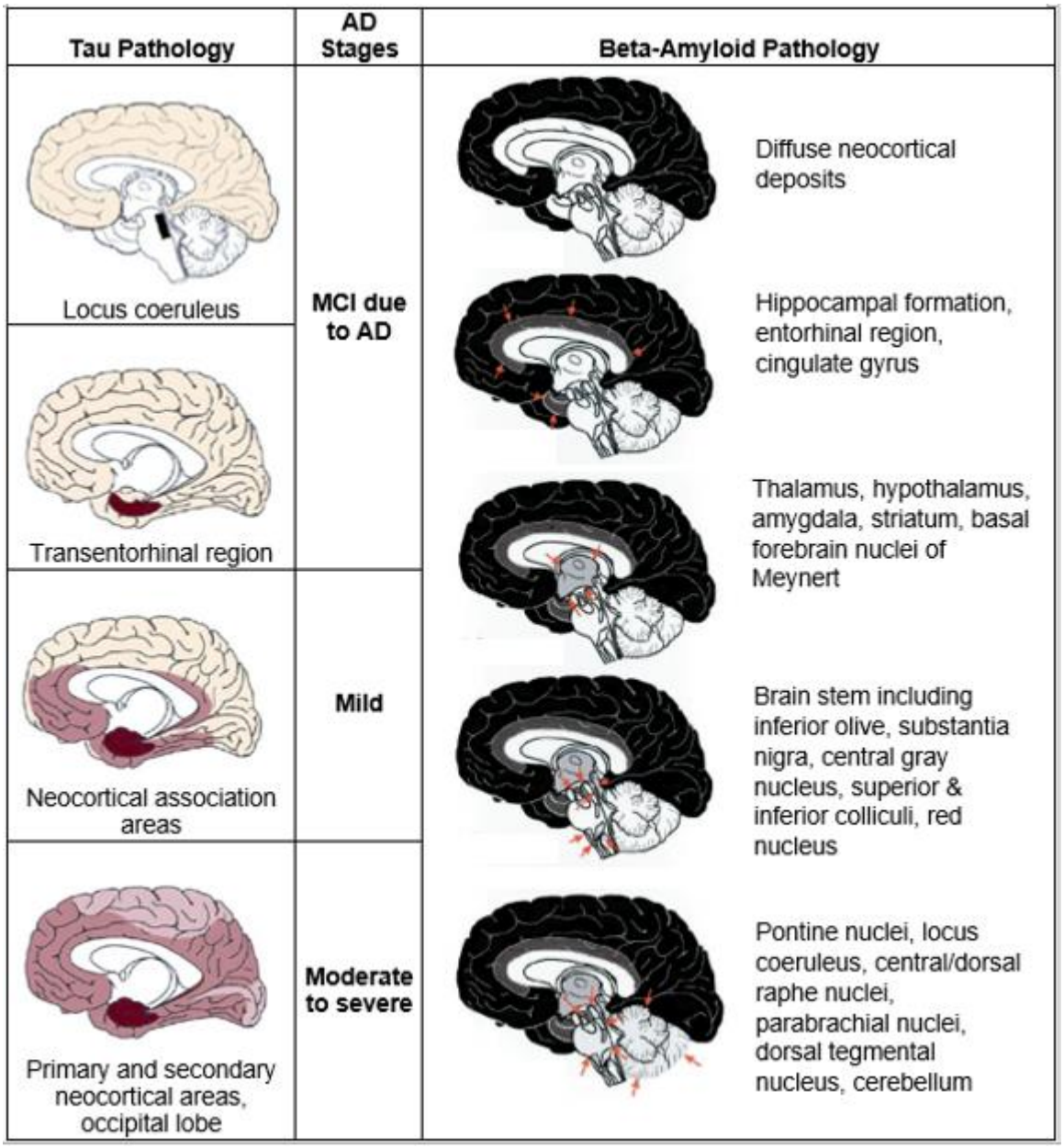

Figure 2. Spread of NFT and Aβ pathology in the brain at different stages of AD.[3] Darker colors indicate greater density of pathology. Red arrows indicate additional Aβ deposits.

[3] Adapted from Braak, H., Thal, D. R., Ghebremedhin, E., & Del Tredici, K. (2011). Stages of the Pathologic Process in Alzheimer Disease: Age Categories From 1 to 100 Years. Journal of Neuropathology & Experimental Neurology, 70(11), 960–969.

1.3 Neuroanatomical structures underlie specific cognitive domains

Neuroanatomical structures affected by AD pathology can be ascribed to specific cognitive domains. The hippocampal formation and locus coeruleus, some of the earliest structures to be affected by AD pathology during MCI, are involved in either learning and memory or functions that subserve learning and memory (Braak et al., 2011). The hippocampus itself is directly involved with learning and memory and is supported by connections both within and outside the MTL. Within the MTL, the hippocampus participates in the intrinsic hippocampal circuit with the entorhinal and transentorhinal regions, the hippocampal formation including the CA1 through CA4 fields of Ammon's horn, and the subiculum (Nieuwenhuys, 2008). The hippocampus is also an integral component of the Papez circuit, which has been found to be critical for episodic memory (Nieuwenhuys, 2008). Intrinsic and extrinsic connectivity of the hippocampus may allow for communication between memory-related structures within the hippocampus as they synthesize vast sensory information from the neocortex (Taylor & Probst, 2008). Lesions involving the hippocampus consistently result in severe episodic memory impairments (Scoville, 1968; Zola-Morgan, Squire & Amaral, 1986; Victor & Agamanolis, 1990), suggesting that integrity of the MTL is necessary for episodic memory function.

The locus coeruleus (LC) is involved in attention and behavioral flexibility (Aston-Jones, Rajkowski & Cohen, 1999). The LC provides mainly norepinephrine (NE)

Adapted from Thal, D. R., Rüb, U., Orantes, M., & Braak, H. (2002). Phases of Aβ-deposition in the human brain and its relevance for the development of AD. Neurology, 58(12), 1791–800.

to cortical and subcortical structures throughout the brain, including the hippocampus (Aston-Jones et al., 1984), and provides particularly dense NE-mediated innervation to structures that are associated with attentional processing such as the parietal cortex, pulvinar nucleus of the thalamus, and the superior colliculus (Morrison & Foote, 1986). The LC-NE system acts to modulate the activity of target neurons (Servan-Schreiber, Printz & Cohen, 1990). Specifically, NE has been found to facilitate the functional integration of attentional systems of the brain (Coull, Buchel, Friston, & Frith, 1999), suggesting that the LC may influence cognitive domains such as memory, by modulating attention (Sara, 2009). NE was also found to have synergistic effects on long-term potentiation (Neuman & Harley, 1983), an electrophysiological marker of learning (Gazzaniga, 2014), suggesting that the LC-NE system is important for long-term memory consolidation (Sara, 2009). This is supported by studies showing lesions of the locus coeruleus results in impaired learning and memory (Anlezark, Crow & Greenway, 1973).

During mild AD dementia, NFT and Aβ have typically expanded to include the frontal, temporal and parietal neocortical association areas involved in executive function with contributions to memory function (Braak et al., 2011). Executive function refers to many sub-functions involved in the planning, initiation and regulation of goal-directed behavior (Lezak, 1983), including attention, inhibition, and working memory. These subdomains also underlie and support complex cognitive domains including memory (Engle, 2002; McCabe et al., 2010). For example, frontal lobe function is often synonymous with executive function, participating in functions including registration, acquisition, or encoding of information (Wagner et al., 1998), free recall of information

without context or other cues (Petrides, 2002), and the recollection of the source of information (Johnson, Kounios & Nolde, 1997) as evidenced by various neuropsychological studies. Disruptions to frontal cortex circuitry lead to deficits in executive function as supported by lesion studies (examples: McAndrews & Milner, 1991; Milner, Petrides & Smith, 1984). Neocortical association cortices are thought to play a role in executive function by consolidating sensory input from primary sensory cortices before projecting these inputs to subcortical structures (Pandya & Yeterian, 1985). Neocortical connections to the hippocampal formation via cingulum bundle also illustrate their contribution to memory (Suzuki & Amaral, 1994; Lavenex & Amaral, 2000).

The neocortical association areas are also involved in semantic memory. Semantic memory refers to stored information of concepts and factual knowledge that cannot be pinpointed to a specific time or event, such as knowing the color of the sky or that tigers have stripes (Budson, 2005). Semantic memory is believed to be diffusely stored in the brain (Hodges & Patterson, 1995), including regions outside of the language network, traditionally thought to be composed of Broca's area on the inferior frontal gyrus, Wernicke's area in the superior temporal gyrus, and the temporo-parietal junction, typically lateralized to the left hemisphere in right-handed individuals (Mesulam, 2001; Nieuwenhuys, 2008). Semantic memory may also be stored in higher-order association areas in the left hemisphere, likely providing intermediary support to the primary language regions (Demasio, 1996; Mesulam, 2016). The view that semantic memory is diffusely stored throughout the brain is supported by the wide projections of the language

network and higher-order association areas throughout the brain (Mesulam, 2001), and by neuroimaging evidence. In healthy individuals, auditory language comprehension has been associated with activity in the left superior, middle, and inferior temporal gyri, left inferior parietal, and left superior prefrontal regions (Demonet et al., 1992). Significant lesions to the language-related regions or circuitry are correlated with prominent language deficits as seen in patients with primary progressive aphasia, whose anomia, word-finding, and comprehension difficulties may be attributed to the disruption of the network involved in semantic processing, retrieval, and word usage (Mesulam, 2001).

During moderate to severe AD, the occipital lobes are one of the few remaining regions to be invaded by NFT and Aβ deposition (Braak et al., 2011), which accounts for the relatively late disturbance of visuospatial abilities in AD patients (Budson & Solomon, 2016). The occipital lobes, like other neocortical regions, are connected to both cortical and subcortical regions. For example, both the peristriate and striate regions of the occipital lobes are involved in the visual processing stream via the inferior longitudinal fascicle (Nieuwenhuys, 2008). Lesions in the occipital lobes have been linked to impairments in visuospatial functions, as seen in rare cases of AD, posterior cortical atrophy (PCA) associated with AD (Benson, Davis & Snyder, 1988). In these unusual AD variant, the visual system is involved first, even in early disease stages and PCA patients typically present with higher-order visual dysfunction involving disturbances of visuospatial, visuoperceptual, visuomotor and visual information processing (for review, see Cronin-Golomb & Amick, 2001). Visual disturbances are

thought to arise due to the disruption in the interaction between cortical information processing systems (Morrison, Hof & Bouras, 1991).

1.4 Neuropsychological tests to assess cognitive capacities

The progression of cognitive impairment observed throughout the stages of AD can be measured using specific neuropsychological tests, which target cognitive domains. Neuropsychological tests provide performance-based measurements of various cognitive domains that can be used in normative comparison across individuals of various ages, educational levels, and backgrounds (Harvey, 2012). According to the Alzheimer's Disease Centers (ADC) program of the National Institute of Aging (NIA), the domains that show the greatest deficits in the neuropsychological profile of AD patients are: attention, speed of processing, executive function, episodic memory and language (Weintraub et al., 2009).

In MCI due to AD, early changes in the hippocampus result in subtle changes in episodic memory (Perry & Hodges, 1999; Chen et al., 2001). The hippocampus is one of the major anatomical structures thought to be involved in episodic memory, along with the surrounding structures of the MTL, basal forebrain, retrosplenial cortex, presubiculum, subiculum, anterior thalamic nucleus, mammillary body, and the prefrontal cortex (Mesulam, 2000). Episodic memory is commonly assessed using the Consortium to Establish a Registry for Alzheimer's disease (CERAD) word list test (Morris et al., 1989). One study found that the summed score across three trials of immediate recall in the CERAD word list learning task was highly sensitive to the presence of MCI due to AD (Karrasch, Sinerva, Grönholm, Rinne & Laine, 2005). The Trails making tests

(TMT) A and B are tests of executive function. TMT A measures processing speed and attention while TMT B measures cognitive flexibility and set shifting (Reitan, 1958). Performance on TMT B has been found to significantly differ between individuals with MCI due to AD and healthy controls (Salmon et al., 2002). Working memory has also been shown to be impaired in MCI due to AD patients (Baddeley et al., 1991).

Impairments observed in mild AD dementia result from alterations in structures of the neocortical association areas, extending to include difficulties with language, in addition to worsening memory and executive function (Price et al., 1993). Mild AD dementia patients perform poorly on CERAD delayed recall, in addition to poor encoding on trials one through three of the CERAD word list learning task (Welsh et al., 1991; Welsh-Bohmer & Mohs, 1997). Mild AD dementia patients also exhibit a rapid rate of forgetting, or the inability to recognize previously seen words within a short period of time (Budson and Solomon, 2016). The presence of a rapid rate of forgetting is highly sensitive to the diagnosis of AD (Flicker, Bartus, Crook & Ferris, 1984; Butters et al., 1988; Knopman & Rybert 1989; Welsh et al., 1991; Tröster et al., 1993) and suggests that AD affects patients' ability to consolidate information as opposed to the retrieval of information (Delis et al., 1991; Weintraub et al., 2012). In the mild AD dementia stage, simple attention as measured by TMT A performance is typically intact, whereas performance on TMT B is often significantly impaired (LaFleche & Albert, 1995). Deficits in language and semantic knowledge are commonly measured by the Boston Naming Test (BNT) (Mack, Freed, Williams, & Henderson, 1992) and verbal fluency tasks (Morris et al., 1989). The BNT is a confrontation naming task and poor

performance reflects the loss of semantic knowledge for particular items (Weintraub et al., 2012). Verbal fluency can be assessed both semantically, where subjects must name as many items that fit within a category in one minute, and phonemically where subjects must name as many items that start with a specific letter as possible in one minute. Mild AD dementia patients typically perform worse on the category fluency task compared to the letter fluency task (Butters, Granholm, Salmon, Grant & Wolfe, 1987; Monsch et al., 1992; Henry, Crawford, & Phillips, 2004). This pattern of verbal fluency performance suggests that AD affects the ability to organize semantic memories, which supports language, rather than retrieval or access of semantic knowledge (Weintraub et al., 2012).

By the time a patient reaches the moderate to severe stages of AD dementia, neuropathological changes extend to include the occipital lobe and primary sensory cortices which result in the alterations in nearly all cognitive domains (Price et al., 1993). During moderate AD, cognitive impairment is present in nearly all aspects of executive function, including working memory and sustained attention (Baddeley et al., 1991). Both TMT A and TMT B time to completion deteriorate significantly in comparison to healthy controls (Greenlief, Margolis, & Erker, 1985). Additionally, significant differences in visuospatial abilities (i.e., by constructional praxis test) are observed in moderate AD (Yuspeh, Vanderploeg, & Kershaw, 1998). As noted by Weinberg and colleagues (2012), the distinction of particularly affected cognitive domains seen early in the course of AD (dark-shaded bars) become difficult to observe during later disease stages (light-shaded bars) (figure 3). By the time a patient reaches severe AD dementia,

he is oriented only to himself and judgment or reasoning may not be possible (Budson & Solomon, 2016).

Neuropsychological tests are considered to be objective measures of cognitive processes. However, the tests often rely upon strongly correlated cognitive components across multiple domains and the specific properties of the tests are often not fully understood (Arnaiz & Almkvist, 2003). For example, attention is commonly required across multiple tests since it aids complex cognitive processes such as memory (Engle, 2002; McCabe et al., 2010); thus, attentional deficits may impair performance on tests of both attention and memory. Furthermore, even when attentional deficits are found, the subtypes of attention are often not easily teased apart by NP tests (Perry & Hodges, 1999). Thus, neuropsychological tests are useful clinically in the staging of AD patients but also contain intrinsic limitations.

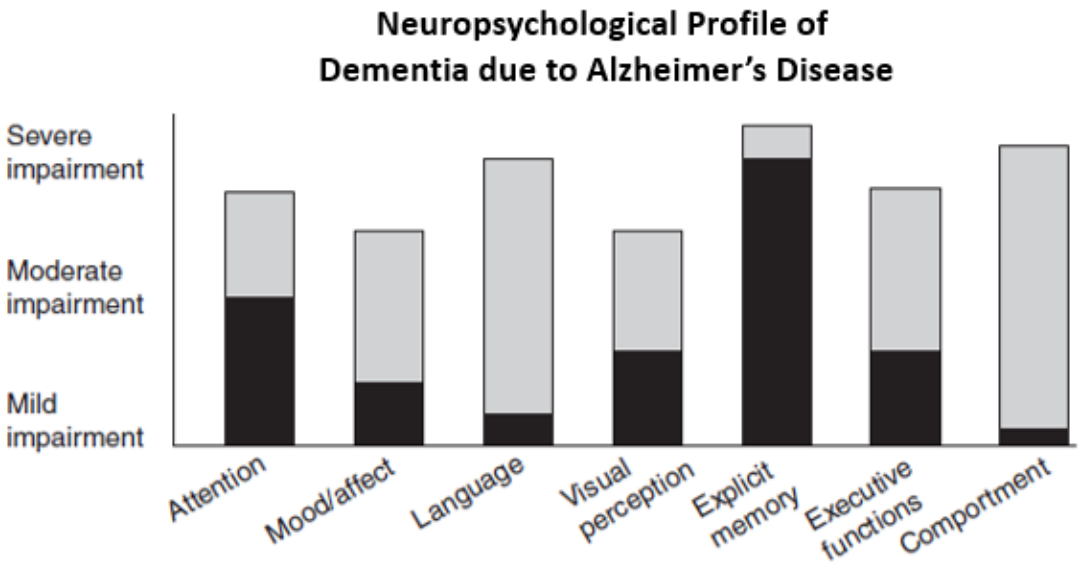

Figure 3. Neuropsychological profile of AD dementia in early versus late stages.[4] Dark bars indicate early AD stages. Grey bars indicate late AD stages.

1.5 Electroencephalogram and Event Related Potentials

Electroencephalograms (EEG) and event related potentials (ERPs) are additional methods of measuring cognitive function generated by specific neural structures. EEGs are a non-invasive neurophysiologic tool that records the global electrical activity of the brain using electrodes placed on the scalp surface (for review, see Kirschstein & Kohling, 2009). EEGs reflect synaptic activity, specifically, the summation of excitatory postsynaptic potentials (EPSPs) and inhibitory postsynaptic potentials (IPSPs). EPSPs and IPSPs in a neuron summate to produce a dipole, or a difference in charge in a neuron. When individual dipoles are produced by many neurons oriented in a similar fashion, a

[4] Adapted from Weintraub, S., Wicklund, A. H., & Salmon, D. P. (2012). The neuropsychological profile of Alzheimer disease. *Cold Spring Harbor perspectives in medicine*, *2*(4), a006171.

net dipole is produced that is strong enough to be conducted through the scalp (Jackson & Bolger, 2014). Ultimately, EEG measures the net dipole of populations of similarly oriented neurons. EEGs provide a physiological measure of cognitive processes and synaptic health, and thus signals vary with cognitive state (Berger, 1969).

ERPs are time-locked, quantitative EEG recordings that measure cognitive responses to specific stimuli. They are recorded as a subject completes a task-related paradigm which involves a series of discrete auditory or visual stimuli. Averaged ERP signals are composed of multiple ERP components, or peaks, that are thought to reflect specific cognitive processes. Whereas EEGs reflect the global electrical activity of the brain, ERPs record changes in brain activity in response to particular tasks. The auditory-oddball ERP paradigm exposes subjects to a series of auditory stimuli, and measures the resultant ERP peaks. P50, N100 and P200 are early sensory responses that are thought to act as a cognitive filter in a mechanism called sensory gating (Golob, Irimajiri & Starr, 2007; Lijffijt, Lane et al., 2009). Sensory gating is a protective mechanism that filters irrelevant sensory information, therefore ultimately modulating, higher-order cognitive processing (Lijffijt, Moeller et al., 2009). A lack of attenuation in sensory gating components in response to a repeated and expected auditory stimulus indicates deficits in sensory processing which may affect higher cognitive processes (Lijffijt, Moeller et al., 2009; Thomas et al., 2010).

The prefrontal cortex (PFC) is thought to be a major generator of P50. Lesion studies of unilateral PFC damage show increased early auditory components (Knight, Staines, Swick, & Chao, 1989). The increased P50 amplitudes seen in PFC lesion patients

are attributed to impaired sensory gating mechanisms (Knigh, Scabini, Woods & Clayworth, 1989; Green et al., 2015).

The auditory cortex of the temporal lobe is thought to be a major generator of N100 (Rogers, Papanicolaou, Baumann, Saydjari, & Eisenberg, 1990) with involvement of the PFC (Knight, Staines et al., 1999). This is supported by the observation of the magnetic equivalent of N100, called the M100, originating in the temporal lobe (Woldorff et al., 1993). N100 peaks were significantly reduced in patients with PFC lesions (Chao & Knight, 1998; Knight et al., 1999).

Strong evidence for a major generator of P200 has yet to emerge; however, the anterior region of the temporal lobes and the frontal lobes are thought to be involved in P200 generation (Rogers et al., 1990). Unilateral lesions of the temporal lobe involving the anterior regions of the superior temporal gyrus resulted in moderately diminished P200 amplitude (Knight, Scabini, Woods & Clayworth, 1988). This is corroborated by statistically significant observations of M200 localized anterior to the auditory cortex (Hari et al., 1987). Frontal lobe is thought to modulate P200 generation (Knight et al., 1988) since frontal lobe atrophy has been highly correlated with P200 amplitude in attentive conditions (McCarley et al., 1989).

N200 and P300 are cognitive ERP components which reflect mechanisms of higher cognitive functioning and occur after approximately 200 milliseconds post-stimulus onset are indicative of higher-order cognitive processing such as attention, memory, and executive function (Olichney, Yang, Taylor, & Kutas, 2011; Yurgil & Golob, 2013). These include N200 and P300 and are called cognitive components. The

N200 is thought to represent early target discrimination in relation to cognitive control which is defined as “the ability to orchestrate thought and action in accordance with internal goals” (Miller & Cohen, 2001). The P300 is thought to reflect an update to the working memory and stimulus categorization (Polich, 2007; Olichney et al. 2011) and can be broken down into the subcomponents: P3a and P3b (Squires, Squires, & Hillyard, 1975).

The cingulate cortex and the temporal lobe are thought to be the major neural generator of the N200. ERP-fMRI evidence localizes N200 to the anterior region of the mid-cingulate cortex (Huster, Westerhausen, Pantev, & Konrad, 2010) and in the middle and superior temporal gyri (Kiehl, Laurens, Duty, Forster, & Liddle, 2001). This is further corroborated by neuropsychological findings that associate N200 peak with inhibition and conflict monitoring (Huster et al., 2010; Botvinick, Cohen, & Carter, 2004), processes which have been linked in part to the cingulate cortex (Botvinick et al., 2004).

Neocortical association cortices are thought to be the neural generators of the P300 peak. The P300 signal can be further divided into P3a and P3b peaks which likely have different neural generators (Polich, 2007). Intracerebral EEG has been used to localize P3a generators in the frontal and temporal lobes, specifically in the dorsolateral prefrontal cortex, supramarginal gyrus, and the cingulate gyrus (Halgren, Marinkovic, & Chauvel, 1998). The same study localized P3b generators to frontal, temporal and parietal lobes, specifically the ventrolateral prefrontal cortex, superior temporal sulcus, posterior

superior parietal lobe, and the medial temporal lobe including the hippocampal and perirhinal cortices.

The localizations of P3a and P3b are further supported by lesion and neuroimaging studies. Lesion studies show that patients with focal hippocampal lesions produced decreased P3a amplitude but normal P3b components (Knight, 1996). Patients with frontal lobe lesions also demonstrated reduced P3a amplitudes (Knight, 1984), supporting the involvement of the dorsolateral prefrontal cortex in P3a generation. Overall, the P300 is generated by a distributed network of the neocortex that suggests that the P300 is involved in a heterogeneous set of cognitive processes (Olichney et al., 2011).

EEGs and ERPs possess high temporal resolution at millisecond intervals, but lack spatial resolution (Jackson & Bolger, 2014). Sources other than the major neural generator of an ERP peak may contribute to the measured signal at the scalp (Jackson & Bolger, 2014). However, ERP components with known neural generators provide valuable link between neuroanatomy and cognitive processes. Given that the pathology at each stage of AD has been well-characterized by histopathological studies, changes in ERPs generated by affected brain regions at each stage of AD can be predicted. The findings may have clinical diagnostic value in the discrimination of AD patients at different levels of clinical severity from non-AD related cognitive impairments.

1.6 Hypotheses

We hypothesized that AD patients would have abnormal ERP amplitudes and latencies for specific peaks versus those values seen in age-matched healthy controls, commensurate with the severity of their AD.

In MCI due to AD, we hypothesized that P3b would be decreased in amplitude given that the MTL is thought to be one of its neural generators, and the MTL is often one of the earliest structures to be affected by AD pathology (Braak & Thal, 2011).

In mild AD dementia, we hypothesized that P50, N100, P200, N200, and P3a in addition to P3b would be observed in abnormal ranges given that wide-spread neocortical association areas involving the frontal, temporal and parietal lobes are impaired at this stage of AD. The neural generator of P50 is in the frontal lobe; N200 in the temporal lobe; P200 and P3a in the frontal and temporal lobes; and P3b in frontal, temporal and parietal lobes. We hypothesized that the N100 would be abnormal because it is highly modulated by neural generators in the frontal lobes (Knight, Staines et al., 1999). Additionally, we anticipated that P50, N100 and P200 would increase in amplitude since they are thought to reflect primarily early sensory responses, rather than cognitive processes, and are thus susceptible to potentially impaired sensory gating in mild AD. We expected P3b to be further decreased in amplitude and increased in latency than the values seen in MCI due to AD given that AD pathology increases in severity in the hippocampus with progression of disease stage.

Finally, in moderate to severe AD, we hypothesized that all ERP components above, P50, N100, P200, N200, P3b, and P3a will show further deviation from normal ranges given that AD pathology increases in density with the progression of disease stage.

METHODS

Ethics Approval

Initial human research study approval was granted by the Department of Veterans Affairs, VA Boston Healthcare System Institutional Review Board from January 25, 2016 to January 24, 2017 under the protocol #2979. A renewal was requested, and approved effective until January 24, 2018. Recruitment of participants officially began in July 2016.

Participants and Initial Screening

Study participants were recruited from the Memory Disorders Clinic at the VA Boston Healthcare System in Boston, Massachusetts. At the time of recruitment, participants were all new patients to the Memory Disorders clinic, aged between 50 and 100 years old, and scored 10 or above on the Montreal Cognitive Assessment (MoCA) (Nasreddine et al., 2005). All patients were either self-referred for memory complaints or referred to the clinic by their primary care physicians for memory problems. As a prospective study, the goal of the experimental design was to recruit participants indiscriminately to explore the extent to which ERPs could be used in a memory clinic population. Participants were not excluded based on comorbid conditions or pharmacological intake, so as to generate a representative sample of patients visiting a memory disorders clinic.

Subjects who agreed to participate scheduled a follow-up appointment with a research assistant within six-weeks of the first clinic visit. Each follow-up appointment

consisted of two-hours of testing including a standard neuropsychological battery (NP) and EEG. All patients gave their informed consent prior to EEG testing. Patients returned to the clinic between three to six months after the initial visit to receive a clinical diagnosis from a behavioral neurologist.

Between July and December 2016, a total of 59 patients consented. Of those, 20 were excluded, 13 of which did not meet the post-EEG inclusion criteria due to low button press accuracy and/or poor audiometry testing, details of which are described below, and six of which discontinued testing due to various reasons. One other subject completed testing but was not included due to issues with ERP recording. Of the 39 participants who did meet inclusion criteria, only 22 had returned to the clinic to receive a diagnosis by the time of this writing. Although gender was not a screening criteria, the majority of the patients seen in the memory disorders clinic were males given the veteran population. Hence, a total of 22 male subjects were included in the data analysis of clinical diagnosis. The demographic information including MoCA scores used for screening is summarized in table 2. Age was the only significantly different factor between non-AD and AD groups (p = .027). Statistical comparison of the global cognitive assessment showed that MoCA and MMSE scores were not significantly different between groups.

Table 2. Demographic data.

Characteristics	Non-AD (n = 13)	AD (n = 9)
Age	72.1 ± 2.09	78.1 ± 1.77* (P = .027)
Education (years)	15 ± 1.01	13.7 ± 0.62
MoCA	22.5 ± 1.16	19.4 ± 1.03
MMSE	27.2 ± 0.60	24.2 ± 1.46

Note: Data are represented as mean ± SEM. *P < .05 compared with non-AD.

Abbreviations: AD, Alzheimer's disease, any stage; MoCA, Montreal cognitive assessment; MMSE, mini-mental state examination; ERP, event related potentials; SEM, standard error of the mean

Inclusion Criteria

After EEG testing, audiometry and button press accuracy (BPA) results for each participant were further examined using the Cognision™ software to determine cutoffs for inclusion in data analysis. Audiometry scores were broken down into hearing thresholds at 1000 Hz and 2000 Hz for each ear. These two frequencies corresponded respectively to the standard and target stimuli used in the auditory oddball paradigm. Patients whose minimum hearing threshold was 80dB in one frequency in both ears or in more than one frequency in either ear were excluded from analysis. Patients whose BPA were below 35% accuracy on the 400-tone auditory oddball task were also excluded from analysis to preserve reliability of the averaged ERP signals.

Study Design: EEG

The EEG equipment was donated by Neuronetrix, but the study was not otherwise funded or sponsored by Neuronetrix. A seven-electrode Cognision™ headset was used to collect EEG data. Cognision™ has been FDA-approved for use in the identification and diagnosis of Alzheimer's disease. EEG activity was recorded from sites Fz, F3, F4, Cz, C3, C4, Pz, P3, and P4 sites on the 10/20 international system (Klem, Luders, Jasper, & Elger, 1958) with reference electrodes on each mastoid process (M1, M2) and one ground electrode on the frontal bone (Fpz) (Figure 4).

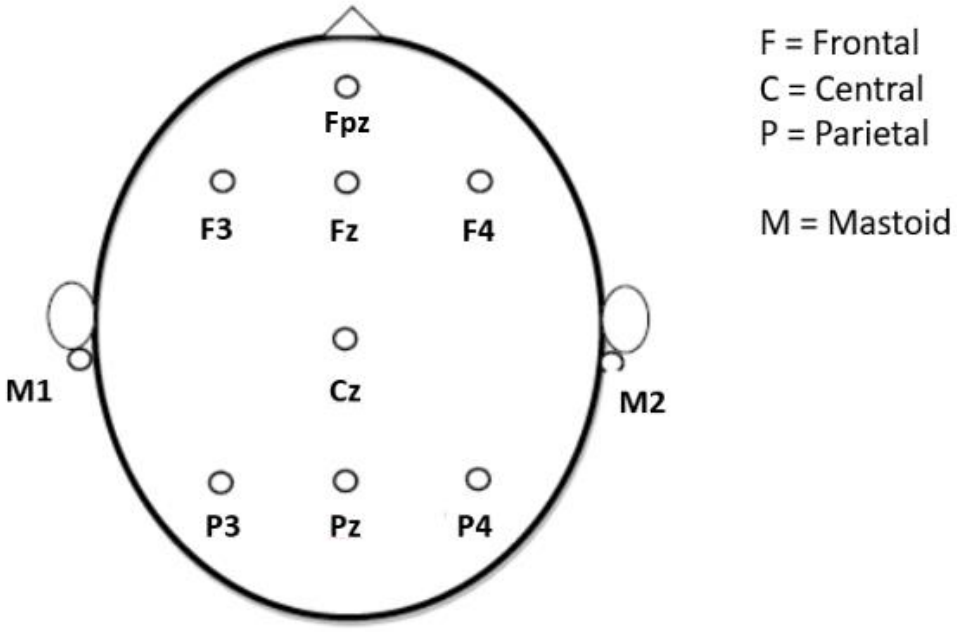

Figure 4. Electrode placement sites for Cognision™

The procedure was split into four parts: an audiometry test, a forty stimuli auditory-oddball practice test, a four-hundred stimuli auditory-oddball full test which

spanned approximately thirty-minutes, and a three-minute resting state EEG recording. Participants first completed an audiometry test, the results of which were automatically used by the Cognision™ software to adjust the tone volume to account for any hearing loss. Participants with audiometry results exceeding 80 dB in either ear did not proceed with further testing.

Next, participants underwent an auditory-oddball paradigm. Stimuli consisted of a 1000 Hz standard tone, 2000 Hz target tone, and a white noise distractor, appearing with 75%, 15% and 10% chance respectively in pseudorandom order. The target and distractor tones were never presented sequentially. The practice session consisted of a forty-trials where a mixture of frequent standard and infrequent target tones were presented through sound-isolating earbuds. Participants were instructed to press a button on the handheld set using their dominant hand each time they heard the higher pitched tone. Participants were corrected during the practice test for errors, and were allowed to take the practice up to three times. EEGs from the practice session were recorded but not used for analysis. If a participant completed the practice session with at least 80% success, he or she moved on to the full task consisting of four-hundred tones that contained a mixture of frequent standard and infrequent target and distractor tones with the same probability of appearance mentioned above. Within the four-hundred total tones of the full length test, there were three-hundred standard, sixty target, and thirty distractor tones appearing in pseudorandom order. Participants were instructed to press the button only if they heard the same high-pitched target tone that was presented in the practice session, but not for other tones, and to press the button as soon as they heard the target tone. If participants

incorrectly pressed the button for the distractor tone, they were reminded to press the button only for the same tone they had heard in the practice. No other corrections were given during the real test. Finally, participants were instructed to sit comfortably with their eyes closed for three-minutes while their resting state EEG was recorded. All EEG testing took place in a quiet room behind closed doors to minimize distractions.

All preprocessing of the EEG data was completed by the Cognision™ software. A single trial (epoch) was defined from approximately -240 ms pre-stimulus to 1000 ms post-stimulus onset. Reaction time (RT) was measured from the onset of stimulus at 0 ms to the time of button press. Peak amplitude was measured in microvolts (μV) between maximum peak amplitude and mean pre-stimulus baseline. Latency was measured in milliseconds between maximum amplitude and stimulus onset. The Cognision™ system software automatically extracted and defined all ERP components. The EEG signal was baseline corrected using the pre-stimulus period. Only the standard tones immediately preceding the target or distractor tones were averaged. Any recordings that exceeded two times the root mean square value were rejected from averaging, as were any false alarms. Only ERPs that averaged more than twenty times after preprocessing (equivalent to BPA of 35%) were included in analysis. The results of the EEGs were automatically generated in a report by the software.

A neurologist categorized each subject based on whether the ERP results seemed consistent with MCI due to AD, mild AD, moderate AD, non-AD or an indeterminate diagnosis given the ranges of ERP values that reflected healthy versus mild AD adults. Since no cutoffs are available that delineate the clinical stages of AD based solely on

ERPs, the ERP evaluations reflect clinical judgement based on the range of healthy versus mild AD conditions by taking into consideration the number of ERP abnormalities and the magnitude of deviation from normal ERP ranges. While evaluating the ERPs, the neurologist was blinded to the patient history and all other clinical measures typically used to diagnose AD. All ERP reports were identified by study codes such that the results could not be traced back to the identity of the participant. The neurologist used an ERP rating form (appendix A) to aid evaluations. The purpose of the ERP rating form was two-fold. First, it served as a reference for the ranges of normal versus abnormal ERP measurements using cutoffs used by Cecchi and colleagues (2015). Secondly, the rating form allowed for clear notation of abnormal components to facilitate quick identification of abnormal ERPs. Raters evaluated seventeen different measures in all, consisting of behavioral measures, peak alpha frequency, and ERP amplitudes and latencies. All abnormal ranges in the mild AD range as previously identified by Cecchi and colleagues (2015), were noted in red on the ERP rating form. Of these, the abnormal measures related to the cognitive components (N200, P3a, P3b) were bolded to indicate greater diagnostic weight relative to the sensory components. The numbers of abnormal indicators in red and abnormal significant indicators in bold were considered by the raters as they categorized each subject as MCI due to AD, mild AD, moderate AD or non-AD using ERP results alone, blinded to the patient history and all other clinical measures typically used to diagnose AD.

Clinical Diagnosis

A neurologist determined the clinical diagnosis for each participant independent of the ERP data at the participant's second appointment at the memory disorders clinic. Per current practice, neurologists take into consideration a patient's medical history, neurological examination, neuroimaging results and the results of the neuropsychological battery to assess whether the memory problems are due to AD or non-AD etiologies. Clinically, the differential of AD is further defined as mild, moderate or severe according to the results of a neuropsychological (NP) battery as well as history of functional decline. NP testing provides objective measures of cognitive functions through the assessment of several cognitive domains. All participants completed a NP battery consisting of the Mini-Mental State Examination (MMSE) (Folstein, Folstein, & McHugh, 1975), Consortium to Establish a Registry for Alzheimer's disease (CERAD) word list test (Morris et al., 1989), trail making tests (TMT) A and B (Reitan, 1958), letter and category word fluency (Morris et al., 1989), and the Boston Naming Test-Short Form (BNT) (Mack, Freed, Williams, & Henderson, 1992; Goodglass, Kaplan, & Weintraub, 1983). Please refer to the introduction for a discussion on the relevance of each test.

The Montreal cognitive assessment (MoCA) and the mini-mental state examination (MMSE) are brief screening tools that provide a global assessment of a patient's cognition. These tests were designed to assess a patient's orientation, registration, memory, attention, language, and constructional praxis in ten minutes for use in practical clinic settings. Both tests are scored out of 30 points where 30 is the perfect

score. At a normal cutoff score of 26, the MoCA has high specificity for differentiating healthy individuals from mild stages of dementia (Nasreddine et al., 2005). The MMSE has greater sensitivity and specificity in differentiating between the later stages of the disease (Nasreddine et al., 2005). No single cutoff score determines the severity of cognitive impairment beyond the MoCA cutoff of 26. Therefore, clinical diagnosis must include the consideration of other aspects of a patient's presentation using clinical judgment (Nasreddine et al., 2005). A range of cutoff scores generally used by clinicians is listed in the table 3. Clinically, it has been observed that AD patients typically decline by 2-3 points in these scores each year (Budson & Solomon, 2016). The MoCA was administered to all new patients as part of a routine clinic procedure during their first visit. The MMSE and other NP exams were administered at a follow-up appointment as part of standard clinical care.

Table 3. Cutoff scores on global cognitive screening tests for the staging of AD (Nasreddine et al., 2005; Budson & Solomon, 2016)

Disease Stage	MoCA	MMSE
Unimpaired	26-30	27-30
Mild cognitive impairment	19-25	24-27
Mild AD	11-21	16-26
Moderate to severe AD	<11	<16

Missing Data

Nineteen cases noted missing values in the measurement for one or more of the following ERPs: P200 standard latency, P200 target amplitude and latency, and N200 target amplitude and latency. Despite the missing amplitude and latencies, the average amplitudes were recorded for all of these cases. Additionally, there was one case in which the system recorded "n/a" across all distractor amplitude, latency and average amplitude and latency. Since the system automatically rejects trials in which a button press error occurred, this was most likely due to the participant pressing the button for all distractor tones during the testing session. Besides this single case, none of the subjects who were missing these measurements were excluded from analysis, in order to retain adequate sample size.

Statistical Analysis

IBM SPSS Statistics, Version 20.0 (IBM Corps, Armonk, NY) was used to conduct all data analyses. Any cases that had missing values were excluded from analyses on a case by case basis. Given the prospective nature of the study design, there was no way to ensure an equal sample size for each of clinical diagnosis. The sample sizes of each diagnostic group was as follows: 1 MCI due to AD, 8 mild AD, 0 moderate AD and 13 non-AD cases. Given the limited number of participants, all AD cases were binned into a single group of n=9. The distribution of the blinded ERP diagnosis of the same cases was as follows: 9 MCI due to AD, 9 mild AD, 0 moderate AD and 4 non-AD cases.

Group comparisons were conducted using the Mann-Whitney U and Krusker-Wallace tests for non-parametric data in age, education, MoCA and MMSE scores (table 4). Age was significantly different between non-AD and AD groups (U=91.5, p=.025) and was used as a covariate in all statistical comparisons where data correlated with age. P values <.05 were considered significant. A Bonferroni correction was applied to all multiple comparisons to control for type I errors and the adjusted P values were reported.

A multivariate ANCOVA was used to determine group differences in the z-scores of ERP measures between clinically diagnosed AD and non-AD groups. Confidence interval was adjusted by Bonferroni method and significant effects of BPA and any significant ERP measurements from multivariate ANCOVA were further examined by bias corrected accelerated (BCa) bootstraps to obtain robust results. The predictive abilities of significant ERP measurements were examined by binary logistic regression

where age was entered as step one and ERP measurements were placed as forced entry inputs with BCa bootstraps.

RESULTS

Table 4. Group comparisons of ERP measures.

ERP Measure	Non-AD (n = 13)	AD (n = 6)
BPA (%)	93.7 ± 2.7	78.14 ± 7.7 * (P = .023)
FA (%)	2.73 ± 1.1	4.77 ± 1.2
Mean RT (ms)	514.80 ± 41.0	516.44 ± 38.9
N100std amp (μV)	-5.57 ± 0.6	-7.74 ± 1.3
P200std amp (μV)	4.91 ± 0.9	4.22 ± 0.7
N100tar amp (μV)	-4.91 ± 0.6	-5.61 ± 1.4
N200tar amp (μV)	-2.37 ± 1.0	-1.03 ± 1.4
N200tar lat (ms)	259.23 ± 10.2	262.23 ± 14.1
P3btar amp (μV)	4.16 ± 1.1	4.29 ± 1.3
P3btar lat (ms)	392.05 ± 20.5	413.48 ± 22.5
P50dis lat (ms)	44.09 ± 3.1	36.69 ± 5.3
N100dis amp (μV)	-3.40 ± 1.4	-7.80 ± 1.6 * (P = .015)
P3adis amp (μV)	7.05 ± 1.0	7.50 ± 2.1

Note: Data are represented as mean ± SEM. *P < .05 compared with non-AD.

Abbreviations: std, standard; amp, amplitude; lat, latency; SEM, standard error of the mean

To examine the correspondence of individual ERP measures and clinical diagnosis, a multivariate ANCOVA [between-subjects factor: clinical diagnosis (non-AD,

AD); covariate: age] was conducted. The test revealed significant effects of BPA, $F(2, 12) = 5.228$, $p = .023$, $\eta_p^2 = .466$, and N100 distractor amplitude, $F(2, 12) = 6.062$, $p = .015$, $\eta_p^2 = .503$ after controlling for the effect of age (figure 5). However, bootstraps for parameter estimates revealed no significant differences in BPA or N100 distractor amplitude in determining non-AD or AD diagnosis. A binary logistic regression with Bias corrected and accelerated (BCa) bootstraps of BPA and N100 distractor amplitude also did not show significance.

To examine whether group differences in N100 distractor amplitude between clinical groups matched the results of the NP battery, Spearman's correlation was conducted (see appendix B for full table). NP results were converted into *z*-scores to allow for standardization of the different units of measurement. N100 distractor amplitude did not significantly correlate with NP battery performance.

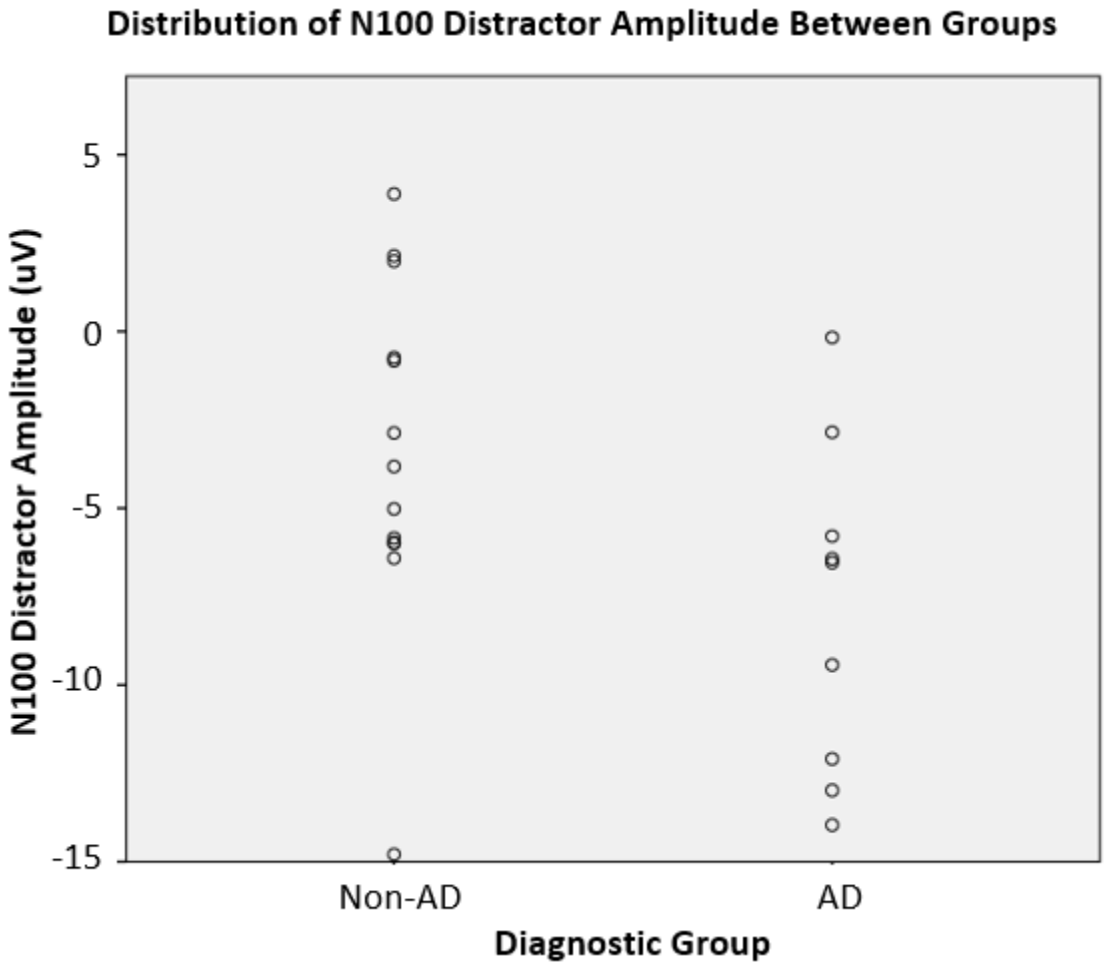

Figure 5. Scatterplot shows distribution of N100 distractor amplitude among AD and non-AD groups.

DISCUSSION

The purpose of this study was to determine whether ERPs can be used as a biomarker of disease severity staging in AD within a heterogeneous group of patients presenting to a memory disorders clinic for initial evaluation. Our results, however limited, emphasizes the complex relationship between the neuroanatomical underpinnings of ERPs. Much work remains to be done to elucidate the clinical utility of ERPs.

We hypothesized that in MCI due to AD, P3b would be abnormal. We did not obtain results that would either support or refute our hypothesis due to small sample size. Previous studies have found P3b with larger amplitude and significantly longer latency in patients with MCI due to AD who later progressed to dementia due to AD than healthy elderly controls (Golob, Irimajiri, & Starr, 2007). However, it is difficult to determine from previous literature whether P3b amplitude and latency would be significantly different between AD and non-AD groups since non-AD pathologies may alter brain regions or networks that coincide with AD pathology at MCI stage.

For mild AD dementia, we hypothesized that P50, N100, P200, N200, and P300 would be abnormal. We found that N100 absolute amplitude to distractor tones was significantly increased in the AD group, which supported our hypothesis and suggested that sensory gating may be more impaired in mild AD dementia than in non-AD related cognitive impairments. The differences in our findings from those in the literature may be attributed to the fact that in this study, N100 amplitude is compared

to a non-AD group rather than healthy elderly controls as in other studies. The pathological changes unrelated to AD that may occur in outside the temporal lobe may still influence the generation of N100 signal. It has been suggested that ERP neural generators are engaged in a complex circuitry modulated by other structures where the loss of a neural generator may result in 1) the compensation of cognitive function by other brain regions, 2) loss of inhibitory or propagating mechanisms that the removed generator may have had on other ERP components and/or 3) the disruption of neuronal synchronicity or organization that may obfuscate ERP signals (Halgren et al., 1986, 1998). This suggestion is supported by the observation of smaller N100 amplitudes in mild AD in comparison to healthy elderly controls (Cecchi et al., 2015, Golob et al., 2007) but greater N100 amplitudes in MCI due to AD (Golob et al., 2007).

For moderate to severe AD dementia, we hypothesized that P50, N100, P200, N200, and P300 components would be abnormal to an even greater extent than seen at mild AD dementia. We did not obtain results that would either support or refute our hypothesis, likely due to small sample size. It is difficult to predict the anticipated result since there are very few ERP studies that include data from patients at moderate to severe stages of AD dementia. Advanced stages of AD dementia profoundly affect function of higher cognition which may impede patients' abilities to follow directions or perform tasks in research studies. Nevertheless, there is evidence from previous studies suggesting that we may not see longer latencies in N100 and P200 in AD compared to non-AD groups which is in contrary to our hypothesis. One study reported normal N100 and P200 latencies during auditory task in an AD group that included severely impaired

patients (Goodin & Aminoff, 1986) and another found no significant differences in N100 latency among patients who presented with a heterogeneous mixture of cognitive impairments (Goodin, Squires, & Starr, 1978). This line of evidence aligns with the histopathological observation that primary sensory cortices are often last to be affected by AD pathology. In fact, it seems unlikely to observe significant changes in N100 and P200 latency between AD and non-AD groups given that primary sensory cortices are not often the direct cause of any cognitive impairment of known etiology.

The interpretations of this study is limited to the comparison of predominantly mild AD to non-AD related cognitive impairment. The decision was made to consolidate the single patient with MCI due to AD with the eight mild AD dementia patients to account for as much as possible the small sample size. Previous studies have had mixed success using ERP to differentiate AD or conversion to AD from non-AD related disorders (Squires, Chippendale, Wrege, Goodin, & Starr, 1980; Gordon, Kraiuhin, Harris, Meares, & Hwson, 1986; Pfefferbaum, Wenegrat, Ford, Roth, & Kopell, 1984; Green et al., 2015). Evidence remains to be seen whether ERP is useful in the diagnosis of the clinical severity of AD from patients presenting with a heterogeneous etiologies of cognitive impairments.

The non-AD group encompassed a wide number of etiologies for cognitive impairment, including neurodegenerative and non-neurodegenerative pathologies (figure 6). A number of these disorders may disrupt brain structures or networks that generate the same ERP components as those disrupted in the different stages of AD. For example, frontotemporal dementia predominantly affects the frontal lobe which may alter ERP

components that may be generated by the region including the P50 and the P3a. However, possibility of multiple etiologies affecting the same ERP components only highlights the need to establish a pattern of abnormal ERP components specific to AD, much as it has been done with the NFT stages, beta-amyloid phases and neuropsychological batteries, to support, or even improve the accuracy of staging AD dementia.

Figure 6. List of clinical diagnoses of participants in the non-AD group. Parentheses indicate the number of subjects that fell into each diagnosis.

Diagnoses within the Non-AD group	
Normal aging (1)	Chronic traumatic encephalography (1)
Possible Lewy body dementia (1)	Multiple sclerosis (1)
Non-AD; normal aging with other psychiatric disease (1)	Depression due to medication and alcohol (1)
Possible frontotemporal dementia, depression (1)	MCI not due to AD (1)
Non-neurodegenerative processes; multifactorial including bipolar disease and prior history of heavy alcohol use. Family history of AD (1)	Etiology yet unknown (4)

Furthermore, the results of this study must be taken with caution due to the lack of statistical power due to small sample size. Statistical power is the probability that a test will avoid committing a type II error. Low power may occur due to small sample sizes, small effect sizes, or both (Button et al., 2013). Low power leads to the overestimation of effect size and low reproducibility of the results. One simple method of avoiding this false positive inflation would be to increase the sample size. Although this

study attempts to control for small power by using the conservative Bonferroni *post hoc* tests whenever possible, larger sample sizes are needed to reduce potential type II errors.

Conclusion

The predictions of this study were driven by previous neuropathological results that show NFT and Aβ pathology disrupt specific neural regions or networks at different stages of AD, thus likely disrupting the ERP signals generated by these neuroanatomical structures. Our results indicate that N100 amplitude may be a promising discriminator of mild AD from non-AD related cognitive impairments. By comparing AD and non-AD groups, the current results of this study highlight the complex relationships between ERPs and their neural generators and their modulation by other regions. Ultimately, although it remains to be seen whether ERPs can successfully discriminate stages of AD within a heterogeneous group of patients presenting to a memory disorders clinic for initial evaluation, we do see promise of utilizing ERPs to deepen our understanding of the relationship between neuroanatomy and disease.

APPENDIX A

Rating form used by neurologists to evaluate ERP results.

Subject Code: _____ Date of Review: _____

Rater Code: _____

EEG Results Rating Form ver 10.3.16

1. Use the patient's EEG report to mark the abnormal ERP features that help you to interpret the results. If the patient's value does not fall in either specified range, please mark the box that best indicates the direction of the deviant feature from normal.

   Red boxes indicate ranges consistent with mild AD.
   Bold boxes indicate the measures of the ERP most helpful in determining mild AD.

STANDARD

	AMPLITUDE			LATENCY			AVG. AMPLITUDE		
	Decreased	Normal Range	Increased	Decreased	Normal Range	Increased	Decreased	Normal Range	Increased
P50	☐	2.69 to 2.85 ☐	☐	☐	44.4 to 45.2 ☐	☐	☐	0.23 to 0.35 ☐	0.54 to 0.66 ☐
N100	☐	-7.37 to -7.09 ☐	-6.14 to -5.86 ☐	☐	92.6 to 93.4 ☐	☐	☐	-4.67 to -4.45 ☐	-3.84 to -3.62 ☐
P200	4.52 to 4.76 ☐	5.12 to 5.40 ☐	☐	☐	213.5 to 215.5 ☐	☐	☐	3.33 to 3.55 ☐	☐

TARGET

	AMPLITUDE			LATENCY			AVG. AMPLITUDE		
	Decreased	Normal Range	Increased	Decreased	Normal Range	Increased	Decreased	Normal Range	Increased
N100	☐	-6.78 to -6.50 ☐	-5.78 to -5.48 ☐	☐	94.7 to 95.7 ☐	☐	☐	-4.37 to -4.13 ☐	-3.55 to -3.31 ☐
N200	-1.26 to -0.94 ☐	-0.48 to -0.14 ☐	☐	☐	249.8 to 252.4 ☐	256.4 to 259.4 ☐	1.80 to 2.06 ☐	2.7 to 2.98 ☐	☐
P3b	4.22 to 4.62 ☐	5.83 to 6.23 ☐	☐	☐	393.2 to 398.8 ☐	416.3 to 422.9 ☐	1.27 to 1.53 ☐	1.76 to 2.08 ☐	☐
Slow Wave	☐	-2.75 to -2.34 ☐	☐	☐	561.1 to 566.1 ☐	572.2 to 578.6 ☐	☐	-0.17 to -0.13 ☐	☐

DISTRACTOR

	AMPLITUDE			LATENCY			AVG. AMPLITUDE		
	Decreased	Normal Range	Increased	Decreased	Normal Range	Increased	Decreased	Normal Range	Increased
P50	3.25 to 3.45 ☐	3.61 to 3.79 ☐	☐	☐	44.6 to 45.8 ☐	47.0 to 48.2 ☐	☐	1.10 to 1.26 ☐	☐
N100	☐	-5.48 to -5.20 ☐	-4.62 to -4.32 ☐	☐	100.6 to 101.6 ☐	☐	☐	-2.95 to -2.73 ☐	-2.33 to -2.09 ☐
P3a	3.43 to 3.83 ☐	5.69 to 6.07 ☐	☐	☐	419.7 to 414.9 ☐	☐	1.13 to 1.39 ☐	3.25 to 3.55 ☐	☐

Number of red boxes (including bolded boxes): _____

Number of bolded boxes only: _____

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