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Evaluation of a Brief Neurometric Battery for the Detection of Neurocognitive Changes Associated with Amnestic Mild Cognitive Impairment and Probable Alzheimer's Disease

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ABSTRACT

Although early detection of cognitive decline associated with Alzheimer's disease (AD) may be critical to successful treatment and prevention, the detection process is complicated by the fact that overt behavioral changes often do not manifest until neurodegeneration is quite advanced. Electroencephalography (EEG) holds promise in this area, and measurements of both resting and event-related brain activity have been identified as potential indicators of cognitive decline. Event-related potential- (ERP-) based markers can be particularly sensitive to functional changes associated with neurodegeneration, but are rendered clinically impractical due to the time required to assess multiple ERP components using standard techniques. This study was designed to evaluate the sensitivity and clinical practicality of a nested neurometric battery for the detection of subtle changes in sensory and perceptual function associated with amnestic mild cognitive impairment (aMCI) and mild AD. The task was well tolerated in a patient sample, and allowed extraction of resting EEG and ERP profiles reflecting multiple neurocognitive domains. Results suggest that profiles of ERP-based measurements may be used to differentiate between individuals at different levels of cognitive impairment, and comparisons of ERP profiles with existing neuropsychological and volumetric data support the potential utility of this procedure in clinical settings.

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Evaluation of a Brief Neurometric Battery for the Detection of Neurocognitive Changes Associated with Amnestic Mild Cognitive Impairment and Probable Alzheimer's Disease

In the context of neurodegenerative disorders such as Alzheimer's disease, earlydetection may be critical to successful treatment and prevention(Sperling et al., 2011). The detection process is complicated, however, by the fact that overt behavioral and cognitive impairments often do not manifest until years after the onset of neurodegeneration(Braak, Braak, & Bohl, 1993; Sperling et al., 2011). Biomarkers of synaptic dysfunction can be utilized to improve the sensitivity and specificity of existing clinical diagnostic criteria, as well as to detect changes associated with Alzheimer's earlier in the course of the disease. Electroencephalography (EEG) holds promise in this area, and the current study was designed to evaluate the prospective utility of an EEG-based neurometric battery for the detection of subtle changes in sensory and perceptual function associated with different levels of Alzheimer's disease-related pathology.

Alzheimer's disease (AD) is a progressive neurodegenerative disorder that develops gradually over the course of many years. Although the process of deterioration is continuous, AD can be divided broadly into three stages: preclinical AD, mild cognitive impairment (MCI), and probable AD (Jack et al., 2011). Preclinical AD consists of asymptomatic presentation with only biomarker-based evidence for the disorder (Sperling et al., 2011). The first overt cognitive and behavioral symptoms mark entry into the MCI stage. Particular emphasis in this stage is placed on amnestic MCI (also referred to as 'prodromal AD' or 'MCI due to AD'), in which the primary symptoms include memory deficits (Albert et al., 2011; Dubois et al., 2010; Dubois & Albert, 2004). The third stage, probable AD dementia, involves functional

deficitssignificant enough to impede daily function(McKhann et al., 2011). As a diagnosis ofAD can only be confirmed following post-mortem neuropathological examination(i.e. for beta amyloid plaques, neurofibrillary tangles, and neuritic plaques;Hyman et al., 2012), references to AD in subsequent pages will be understood to refer to probable AD.

Biomarkers of AD

Commonly studied markers of ADinclude levels of beta amyloid (Aβ42), tau, and phosphorylated tau in cerebrospinal fluid (CSF; Blennow et al., 2015), amyloid imaging and fluorodeoxyglucose (FDG) uptake measured with positron emission tomography (PET; Mosconi et al., 2010), and atrophy in certain brain structures (e.g. medial temporal atrophy) observed using structural magnetic resonance imaging (MRI; Bocchetta et al., 2015). Although not yet approved or recommended for use in clinical practice, there is general consensus surrounding the importance and potential utility of physiological markers of Alzheimer's disease(de Souza et al., 2014; Fiandaca, Mapstone, Cheema, & Federoff, 2014; Forlenza, Diniz, Teixeira, Stella, & Gattaz, 2013; Gomar et al., 2011; McConathy & Sheline, 2015; Risacher & Saykin, 2013; Sperling & Johnson, 2013; Weiner et al., 2012; Wurtman, 2015).The FDA has expressed support, although not official approval, for thedevelopment and use of markers such as hippocampal volumeand CSF levels of Aβ42, tau, and phosphorylated-tau (U.S. Food and Drug Administration Center for Drug Evaluation and Research, 2015a, 2015b), andincorporation ofbiomarkersis recommended for research purposes in the revised guidelines of 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).

Although the most frequently utilized biomarkers can be highly effective adjuncts to traditional diagnostic criteria, common techniques for biomarker assessment have the disadvantages of being invasive (CSF), expensive (PET,MRI), and/or requiring specialized facilities or personnelto administer (CSF, PET, MRI; Humpel, 2011; Luck, 2014). The value of reliable detection compensates for these disadvantages, but these procedures are not ideal candidates for use asscreening tools in the general population. EEG, which presents a complementary set of advantages and disadvantages to these techniques,may be better suited to this purpose.

Utility of EEG

EEG involves the recording at the scalp of voltage changes due to patterns of cortical activity (summated changes due to large groups of neurons firing together; Luck, 2014). Sensitive to neurotransmission-related electrical activity, EEG has a high temporal resolution which renders it capable of detecting subtle alterations in neural responses to different contexts. Compared to existing biomarkers which directly assess physiological changes, EEG recordings provide more functional information. In clinical settings, EEG recording techniques have certain features which complement existing biomarker assessment techniques (CSF, PET, MRI).In particular, EEG is noninvasive, relatively inexpensive, and involves flexible, mobile equipment that can be easily used with a moderate amount of training.

Two principal types of activity in an EEG recording include ongoing rhythmic oscillatory activity (continuous activity in various frequency bands reflecting

synchronous firing of groups of neurons) and event-related activity. Patterns of baseline oscillatory activity can be assessed from recordings of continuous EEG during periods of rest.In resting-state designs, participants sit motionless for several minutes while brainactivity is recorded. This technique has the advantages of being task-independent and patient-friendly, and assessments of power in different frequency bands[1]can be sensitive togeneral neurological changes(Moretti et al., 2004; Rossini et al., 2008).For example, a progressive 'slowing' of neural oscillatory activity has been reported in patients with AD, manifesting as an increased proportion of activity inthe lower delta (0.5-4 Hz) and theta (4-8 Hz) frequency bands (Babiloni et al., 2014; Forstl et al., 1996; for a review, see Jackson & Snyder, 2008).The spectral composition of resting oscillatory activity can be used as a marker of underlying pathology and has been suggested for use in screening for AD(Bennys, Rondouin, Vergnes, & Touchon, 2001; van Straaten, Scheltens, Gouw, & Stam, 2014; Vecchio et al., 2013).

Event-related potential components. The second principal type of activity in EEG recordings, event-related activity, involves isolation oftransient activity that occurs in response to an event or stimulus.Event-related potentials (ERPs) are derived from averages of responses to similar events over many trials (such that ongoing oscillatory activity is cancelled out) and are thought to reflect neuronal activity specific to the processing of a particular event (Luck, 2014).[2]ERP waveforms are time-locked to event onset, and manifest as a series of peaks and troughs in the milliseconds (ms) immediately following (or preceding, in some cases) the event. Components of interest are identified

[1] Various aspects of cognition have been associated with oscillatory activity over different areas of the cortex in each of the standard frequency bands (delta, 0.5-4 Hz; theta, 4-8 Hz; alpha, 8-13 Hz; beta, 13-30 Hz; and gamma, 30-80 Hz; Kahana, 2006).

[2] Event-related activity can also include event-related oscillations, which reflect synchronization of oscillatory activity in the milliseconds surrounding a particular event.

using acronyms or numbers/letters indicating the direction of the component and its relative position in the waveform (N1 indicates the first negative peak, and P2 indicates the second positive peak, for example).

Whereas assessments of continuous oscillatory activity provide information regarding ongoing processes, ERP-based analyses provideinformation regarding performance of specific tasks, allowing assessment of the integrity of various domains of functioning. Although poor spatial resolution limits the utility of ERPs for localization, millisecond temporal resolution renders these measurements sensitive to changes in sensory, perceptual and cognitive processing (Luck, 2014). ERP components can be used to detect functional impairments in clinical populations(Kappenman & Luck, 2012; Luck, 2014; Luck et al., 2011), and have prospective value not only as biomarkers of neurocognitive dysfunction associated with AD (Jackson & Snyder, 2008; Olichney & Hillert, 2004; Olichney, Yang, Taylor, & Kutas, 2011; Verleger, 2012), but also as markers of risk of conversion from MCI to AD(Chapman et al., 2011; Missonnier et al., 2007; Missonnier et al., 2005; Olichney et al., 2008; Papaliagkas, Kimiskidis, Tsolaki, & Anogianakis, 2011).

Variations associated with AD have been observed in a range of ERPs reflecting a variety of processes, including working memory (Chapman et al., 2007, 2011, 2013; Missonnier et al., 2007; Missonnier et al., 2005), early visual processingand motion detection (Fernandez, Kavcic, & Duffy, 2007; Stothart, Kazanina, Näätänen, Haworth, & Tales, 2015), early auditory processing (Golob, Irimajiri, & Starr, 2007; Golob, Johnson, & Starr, 2002; Irimajiri, Golob, & Starr, 2005; Jessen et al., 2001), attentional control and stimulus classification (Bennys, Portet, Touchon, & Rondouin, 2007; Golob et al., 2002;

Gozke, Tomrukcu, & Erdal, 2013; Lai, Lin, Liou, & Liu, 2010; Papaliagkas et al., 2011; Polich, Ladish, & Bloom, 1990; Polich & Corey-Bloom, 2005; Smart, Segalowitz, Mulligan, & MacDonald, 2014), semantic congruity and encoding/retrieval processes related to word repetition (Olichney et al., 2002; Olichney et al., 2008; Olichney et al., 2006), selective attention(Cespón, Galdo-Álvarez, & Díaz, 2013),motor preparation(Cespón et al., 2013; Cespón, Galdo-Álvarez, Pereiro, & Díaz, 2015) and performance monitoring (Mathalon et al., 2003). The literature in this area is diverse and fragmented, with a number of candidate biomarkers identified for potential clinical use. Given the diversity of ERPs and processes found to be affected in AD, designs which allow assessment of multiple distinct processes or systems may prove useful for comparing the relative utility of different combinations of ERP markers.

The importance of multidimensional ERP assessment is even more apparent when consideringcomponents like the auditory oddball P3. The auditory P3 has been extensively studied in Alzheimer's disease, withP3 latency found to predict neurocognitive dysfunction(Pedroso et al., 2012; Polich & Corey-Bloom, 2005). However, this component has also been shown to vary in similar ways in a variety of other populations (Dejanović et al., 2015; Ortiz, Martin Loeches, Miguel, Abdad, & Puente, 1994; Polich & Herbst, 2000; Qiu, Tang, Chan, Sun, & He, 2014; Simons et al., 2011; Urretavizcaya et al., 2003). As a marker, auditory P3 latency appears highly sensitive but non-specific(Polich & Herbst, 2000). Todifferentiate P3 abnormalities due to AD from abnormalities due to other conditions, assessment of additional components reflecting other neurocognitive dimensions is likely to be necessary.

Limitations to use of ERPs in clinical settings. Although ERP-based techniques have prospective utility as physiological markers, several limitations currently hamper their application in clinical settings. Steps are being taken to improve standardization and surmount issues related to reliability, quality control, and individual variation (Luck et al., 2011). Additional limitations involve the structure of cognitive tasks designed to elicit ERP-based markers, and include the time required for assessment and the demands placed on the patient.

In order to isolate the neural activity associated with a specific event, ERP-based tasks require the averaging of responses to a large number of (nearly) identical trials. It can take over 20 minutes of recording to effectively isolate a single ERP component or process, and this typically involves performance of a repetitive cognitive task. Although a 20-minute recording period is clinically reasonable, variations in ERP-based markers along a single dimension are unlikely to be sufficient to adequately characterize AD and differentiate it from other forms of dementia.

As discussed in the previous section, a profile of ERP-based measurements reflecting a range of neurocognitive processes would be a more efficient (and potentially more powerful) tool for detection and characterization (Kappenman & Luck, 2012). However, to obtain a profile of measurements in a single recording session using standard recording techniqueswould involve the completion of several consecutive cognitive tasks, each designed to isolate a particular component or process.This serial presentationwould quickly result in a recording period of clinically impractical duration, in addition to

placing unrealistic demands on the resources of the participant(Kappenman & Luck, 2012).[3]

Addressing limitations. Kappenman and Luck (2012) have proposed a solution to this problem in the form of a design in which ERPs reflecting multiple neural systems can be assessed in parallel through use of factorial combinations of stimuli and difference waves. In their study, they propose a design in which multiple components can be measured in the context of a 40-minute task using a single, multi-part visual display. By using factorial combinations of visual stimuli withina single trial, this task canbe used to simultaneously elicit multiple ERPs reflecting distinct neurocognitive processes. The use of difference waves, in which responses to one type of stimulus are subtracted from responses to another type of stimulus, allows the isolation of differences in activity associated solely with differences in the stimuli under consideration.

In the auditory domain, researchers have demonstrated that stimuli designed to elicit multiple auditory ERP components can be nested within a single auditory stimulus train(Hershaw, 2013; Näätänen, Pakarinen, Rinne, & Takegata, 2004; Pakarinen et al., 2009). Uniting these two auditory and visual frameworks in a previous study, we were able to demonstrate that a task in whicha modified version of Kappenman and Luck's (2012) procedure was integrated with a nested auditory stimulus traincould evoke aprofile of distinct ERP components that could be used to detect differencesin processing associated with normal aging(Kieffaber, Hershaw, & Cunningham, In Preparation).

This task was designed to elicit a multidimensional profile of ERP components in as brief a recording session as possible, for clinically practical detection of subtle changes

[3] Certain cognitive tasks (N-back working memory tasks, e.g.) can place significant demands on the resources of the participant regardless of the time required. Even simple tasks can induce fatigue after 20 minutes or more of repetition.

in sensory, perceptual, and cognitive function.The design permits the assessment of nine distinct components representing different neurocognitive processes in a period of approximately 25 minutes (including two minutes of resting-state recording as well as three practice rounds). In addition to resting-state oscillatory activity, this task can be used to assess P50 suppression, mismatch negativities to both frequency and inter-stimulus-interval (ISI) deviation, and visual mismatch negativity, C1, N2pc, P3, lateralized readiness potential, and error-related negativity components. These components are briefly reviewed in the following sections.

P50 suppression and sensory gating. The P50 component is identified as a frontocentral peak in the auditory waveform with onset approximately 50 ms following the presentation of a tone. P50 suppression is typically assessed in the context of a paired-click paradigm, in which stimuli consist of pairs of clicks presented in rapid succession(Dalecki, Croft, & Johnstone, 2011). In healthy adults, P50 amplitude following the second click is typically reduced relative to P50 amplitude following to the first, and this suppressionis thought to reflect integrity of automatic sensory gating processes, or the ability to filter out (gate) extraneous stimuli(Adler et al., 1982). Abnormalities in P50 suppression have been commonly observed in patients with schizophrenia(Adler et al., 1982; Potter, Summerfelt, Gold, & Buchanan, 2006), and have also been linked with other conditions, including AD (Jessen et al., 2001), and panic disorder (Ghisolfi et al., 2006).

Auditory mismatch negativity. The auditory mismatch negativity (MMN) refers to a change-specific, attention-independent frontocentral negative deflection in the auditory waveform that is typically observed 150-250 ms following a stimulus that deviates from a

standard auditory train(Näätänen, Gaillard, & Mäntysalo, 1978). Thought to reflect processes associated with stimulus discrimination and auditory sensory memory, the MMN can be elicited by any deviation in a standard auditory stimulus train, including deviations in frequency, duration, intensity, and inter-stimulus interval (ISI; Näätänen, Paavilainen, Rinne, & Alho, 2007). Abnormalities in the auditory MMN have been reported in a variety of populations, and attenuated MMN amplitude has been suggested as a potential marker of psychosis(Light & Näätänen, 2013; Risto Näätänen, Shiga, Asano, & Yabe, 2015) and amnestic MCI (aMCI; Lindín, Correa, Zurrón, & Díaz, 2013).

Visual Mismatch negativity. The visual mismatch negativity (vMMN) is thought to be an analogue of the auditory mismatch negativity, and is elicited in response to deviations (in stimulus orientation or apparent motion direction, e.g.) in a standard train of visual stimuli(Pazo-Alvarez, Cadaveira, & Amenedo, 2003). Typically maximal over occipital electrodes, the vMMN manifests as a negative deflection in the visual waveform observed in approximately the same post-stimulus window as the auditory MMN, and is thought to index processes related visual sensory memory and stimulus discrimination(Näätänen et al., 2007; Pazo-Alvarez, Amenedo, & Cadaveira, 2004; Pazo-Alvarez et al., 2003). Abnormalities in thevMMNhave been noted ina range of clinical populations, including AD (Stothart et al., 2015; Tales, Haworth, Wilcock, Newton, & Butler, 2008), and have been suggested as prospective markers of cognitive decline (Maekawa, Hirano, & Onitsuka, 2012; Stothart et al., 2015).

*C1.*The C1 component is an early component of visual evoked potentials with a central occipital-parietal distribution. The C1 component is typically maximal in the 50-100 ms following stimulus onset, and polarity of the component is largely dependent on

the vertical position of the stimulus in the visual field, with stimuli in the upper visual field typically eliciting a negativity and stimuli in the lower visual field eliciting a positivity (Clark, Fan, & Hillyard, 1994). Thought to index integrity of early visual processing, limited information exists regarding variation of the C1 component in clinical samples, but reductions in C1 amplitude have been observed in normal aging(Kappenman & Luck, 2012).

*N2pc.*The N2pc component, a posterior negativity in the visual waveform contralateral to the location of a target stimulus ('pc' stands for 'posterior-contralateral'), is thought to reflect selective attention, and is elicited using lateralized stimuli in the presence of distractors(Luck & Hillyard, 1994). With typical onset in the range 200-300 ms post-stimulus, the N2pc can be isolated by subtracting ipsilateral from contralateral waveforms to create a difference wave (Kappenman& Luck, 2012). Attenuation of the N2pc component have been associated with aMCI (Cespón et al., 2013).

P3. Perhaps the most commonly studied component, the P3 refers to the third major positive peak in a stimulus-evoked waveform, with onset beginning approximately 300 ms post-stimulus(Picton, 1992). Maximal over parietal areas, the P3 component is typically assessed in the context of oddball tasks, and is observed to have greater amplitude following rare than common targets. The oddball P3 is thought to reflect task-related attentional processes, and abnormalities in oddball P3 have been observed in many samples, including patients with AD (Pedroso et al., 2012), all-cause dementia (Ortiz et al., 1994), psychosis (Simons et al., 2011), and stroke (Dejanović et al., 2015).

Lateralized readiness potential. The lateralized readiness potential (LRP) is a response-related ERP component thought to reflect motor preparation processes(de Jong,

Wierda, Mulder, & Mulder, 1988; Gratton, Coles, Sirevaag, Eriksen, & Donchin, 1988). Typically maximal in electrodes over the motor cortex during the 200 ms immediately preceding a response, the LRP is observed as a negativity in the waveform contralateral to the responding effector, and is evaluated relative to the corresponding ipsilateral waveform (isolated with difference waves; Smulders & Miller, 2012). Abnormalities in the LRP have been linked to schizophrenia (Luck et al., 2009)and AD (Cespón et al., 2013, 2015).

Error-related negativity. The error-related negativity (ERN)is a response-related ERP component thought to reflect implementation of detection and control processes following the commission of an error(Falkenstein, Hohnsbein, Hoormann, & Blanke, 1991; Gehring, Goss, Coles, Meyer, & Donchin, 1993). Typically observed in the 100 ms immediately following a response in a speeded-choice response task, the ERN manifests as a large frontocentral negative deflection following errors (relative to correct responses; Gehring, Liu, Orr, & Carp, 2012). Amplifications of the ERN have been observed in anxiety disorders (Olvet & Hajcak, 2008), and attenuations of the ERN have been linked to schizophrenia (Hasey& Kiang, 2013) and AD (Mathalon et al., 2003).

The Current Study

The current study was designed to test the sensitivity and clinical practicality of a nested neurometric battery for use in the context of AD and MCI. Our goals were (a) to demonstrate that older adults with varying levels of cognitive impairment could tolerate and successfully complete the task, (b) to evaluate the sensitivity of this tool for the detection of differences associated with different levels of AD-related symptomology, and (c) to compare this profile with existing volumetric and neuropsychological

assessments. We posited that a brief (25-minute) session would optimally balance recording time with participant fatigue, and that a two-choice speeded response task would be simple enough not to frustrate or tax the resources of participants during this time-period. Although we adopted no specific hypotheses regarding the behavior of individual EEG/ERP measurements in our sample, we did expect that a multivariate comparisons of EEG/ERP profiles would significantly differentiate participants with aMCI from those with AD, and that relevant predictors in these profiles would relate to existing neuropsychological and volumetric (e.g. hippocampal volume, hippocampal occupancy score) information.

Method

Participants

Data were obtained from thirty older adults recruited from an outpatient memory clinic. Participants were patients diagnosed with either aMCI (n = 13) or probable AD (n = 17) according to revised NIA-AA criteria (McKhann et al., 2011), and were screened for history of other neurological conditions (e.g. stroke, seizure disorder, traumatic brain injury) prior to participation. 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.All participants received financial compensation for participation.Twelve participants (aMCI: n = 1, AD: n = 11) werebeing treated with cholinesterase inhibitors(donepezil) at the time of participation, and two participants with AD had also been prescribed the NMDA receptor agonist memantine.[4]Hearing aids were worn by three participants. Four participants with incomplete data resulting from

[4] The possibility exists that psychotropic medications could interfere with effective electrophysiological assessment, but there is some evidence to suggest that the effects of these drugs on ERP biomarkers are minimal (Chapman et al., 2013).

technical issues during data collection (n = 2) or requests to discontinue (n = 2) were excluded from analyses. An additional seven participants were excluded from analyses due to poor task performance (see Results). Demographic information forthe remaining 19 participants is presented in Table 1.

Materials and Design

The Montreal Cognitive assessment (MoCA), a brief, comprehensive screening tool designed to be sensitive to early changes across major cognitive domains, was used to assess global cognitive function (Nasreddine et al., 2005). 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.

Surrogates also completed the AD8 dementia screening interview, a subjective, informant-based screening tool designed to assess perceived changes in cognitive function (Galvin et al., 2005). The AD8 is an eight-item questionnaire with a clinical cutoff of two (affirmative responses on two or more items indicate probable presence of cognitive impairment).

Vision and hearing assessments were conducted using a Snellen chart and the Hearing Handicap Inventory for the Elderly-Screening Version (HHIE-S; Ventry & Weinstein, 1982), respectively. The HHIE-S is a 40-point, 10-item questionnaire assessing the emotional and social 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 Battery. The electrophysiological battery was programmed in MATLAB (R2012b; TheMathworks, Inc., Natick, MA). Prior to presentation of task instructions, one minute of eyes-open and one minute of eyes-closed resting EEG activity were recorded. Task instructions were presented on-screen and reviewed verbally with the participant to ensure comfort with the requirements of the task. In addition, three progressive practice rounds of 10 trials each were provided. The first round consisted solely of target stimuli; additional visual stimuli were added in the second round; and auditory stimuli were incorporated in the third round. The battery contained 400 total trials with a self-timed break provided after 200 trials.A schematic of the task is presented in Figure 1.

Auditory stimuli. Stimuli nested within a single auditory stimulus train were used to elicit P50 and MMN components. Auditory stimuli consisted of standard tones (500 Hz sinusoidal tones with a duration of 100 ms), deviant tones (1000 Hz sinusoidal tones with a duration of 100 ms), and sets of paired clicks (1 ms square-wave tones) with the first click separated from the second by a fixed interval of 250 ms.Stimuli were presented binaurally using around-ear headphones adjusted to 70 dB.

Auditory stimulus train. A series of standard tones presented at consistent intervals of 2600 ms formed the base of the auditory train. In orderto elicit a Gap MMN, standard tones were presented at an abbreviated ISI of 1300 ms(15% of trials).To elicit a Frequency MMN, the standard tone was replaced by a deviant tone at the regular, 2600 ms ISI (another 15% of trials). A total of 310 standard tones were presented at the standard ISI, 60 standard tones were presented at the abbreviated ISI, and 60 deviant tones were presented. P50 suppression was elicited using click pairs nested within a

subset of 90 trials, with the first click beginning at a random point in the interval 1600-2250 ms following trial onset (see Figure 1).

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°. A 1500- by 250-pixel rectangular sine grating with a spatial frequency of 0.011 cycles per pixel (90 pixels per cycle) was displayed in either the upper or lower portion of the screen during each trial. To give the appearance of motion either to the left or right, the grating phase was adjusted by 36 pixels on each refresh. 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.

Task design. 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'"), and to respond using the left and right control buttons on a standard QWERTY keyboard (allowing measurement of the LRP). Assignment of keys to targets was randomized across participants. In addition, the design was counterbalanced such that 50% of participants were directed to respond to letters, and 50% were directed to respond to numbers. No feedback was provided to participants regarding the accuracy of their responses.

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 P3. Stimuli in the distractor set were evenly distributed such that each of the two distractors was presented on 50% of trials. The position of target and

distractor stimuli was pseudorandomized across trials such that participants had to shift attention laterally depending on the location of the target, allowing isolation of the N2pc.

For the visual grating, a standard motion direction (left or right) was randomly assigned for each participant. To elicit a vMMN to change in motion direction, gratings of deviant motion direction were presented on 13% of trials. The position of the grating was pseudorandomized such that it appeared either at the top or bottom of the visual field with equal probability across trials, allowing isolation of the C1 component.

During each trial, auditory and visual stimuli were presented over a 2600 ms interval with no overlap (for timing details, see Figure 1B). A total of 400 trials were presented in pseudorandomized order, and visual stimuli were factorially combined such that the probability of one type of stimulus was independent of the probabilities of other stimuli. Visual trials could be subdivided into 340 high- and 60 low-probability targets; 200 left- and 200 right-lateralized targets; 348 high- and 52 low-probability motion direction trials; and 200 upper and 200 lower visual grating trials.

The ERN component could be isolated by comparing correct and incorrect responses to target stimuli. In order to encourage an appropriate number of errors, the task was designed such that a feedback message appeared every 40 trials. In addition to a reminder of correct key-target assignment, the message "Please try to respond more accurately" was displayed if the error rate exceeded 20%, and the message "Please try to respond more quickly" was displayed if the error rate was lower than 10%.

Procedure

Participants were invited to take part in the study at the conclusion of a scheduled visit to the clinic. Once participants and surrogates provided assent and informed consent,

respectively, participants were administered the MoCA, hearing, and vision assessments, and surrogates were asked to complete the AD8. 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.

Structural MRI information was available for a subset of participants who participated in the scans as part of their standard workup. These scans took place on a different date and at a different location from the EEG recording.

MRI Acquisition and Analysis

Structural MRI data were available for a subset of 16 participants. Four of these participants were excluded from final analyses, leaving 12 participants with MRI information. Volumetric data were obtained from high-resolution 3D scans analyzed using FDA-approved, fully-automated NeuroQuant® software (CorTechs Labs, Inc., San Diego, CA). Absolute and relative volumes of medial temporal lobe structures (hippocampus, lateral ventricle, inferior lateral ventricle) were obtained for each participant.Medial temporal atrophy was also assessed using a ratio of hippocampal volume to the sum of hippocampal and inferior lateral ventricle volumes.

EEG Recording & 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 froman extended 10/20 cap system with 28 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 (The Mathworks, Inc., Natick, MA) using EEGLAB (Delorme & Makeig, 2004) and ERPLAB(Lopez-Calderon & Luck, 2014) toolboxes. Raw data were resampled to 1000 Hz and an initial IIR Butterworth 0.1-100 Hz band-pass filterwas 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 = 0.96, SD = 1.54). Ocular artifacts were identified and removed using independent component analysis (ICA; Jung et al., 2000).

ERP profile. Following artifact removal, an additional IIR Butterworth band-pass filter was applied. For analyses of the P50 component, a filter of 10-50 Hz was used. Data were segmented into stimulus-locked epochs of -100 to 500 ms surrounding stimulus onset and baseline-corrected over the pre-stimulus interval. Trials containing voltages in excess of +/- 50 μV were removed (Dalecki et al., 2011).

For the remaining ERPs of interest, a filter of 0.5-20 Hz was applied.[5] For Frequency and Gap MMNs, vMMN, C1, N2pc, and P3 waveforms, data were segmented into stimulus-locked epochs of -200 to 1000 ms surrounding stimulus onset and baseline corrected over the pre-stimulus interval. For response-related ERP components (LRP and ERN), data were segmented into response-locked epochs of -600 to 1000 ms surrounding stimulus onset and baseline corrected over the interval from -600 to -400 ms. Trials containing voltages in excess of +/- 100 μV were removed.

[5] A high-pass cutoff of 0.5 is higher than recommended for typical ERP studies (Luck, 2014), but more restrictive cutoffs may be applied for clinical samples (e.g. Lee et al., 2013; Smart, Segalowitz, Mulligan, & MacDonald, 2014).

To eliminate potential effects of rare/oddball stimuli on the measurement of other components, the following adjustments were made: (a) trials containing rare targets were excluded from vMMN, C1, N2pc measurements, (b) trials containing vMMN deviants were excluded from P300, C1, and N2pc measurements, and (c) responses following P3 targets were excluded from ERN and LRP measurements. In addition, the possibility of interactions between auditory and visual stimuli was evaluated by (a) comparing mean amplitudes within subjects for visual trials in which auditory events were present in a window 1000 ms pre-stimulus with those of identical visual trials not preceded by auditory events; (b) comparing mean amplitudes of auditory trials where visual events of different types were present in a 1000 ms pre-stimulus window with those of identical auditory trials not preceded by visual events; and (c) comparing mean amplitudes of auditory trials where auditory events were present in a 1000 ms pre-stimulus window with those of identical auditory trials not preceded by other auditory events. No statistically significant audiovisual interactions were observed for any subset of visual or auditory trials (all $p > .05$). However, presence of standard auditory stimuli in the 1000 ms pre-stimulus window did significantly affect P50 S1 amplitude, $t(18) = -2.32$, $p = .032$. Given this information, as well as observations that P50 suppression is sensitive to proximate auditory stimuli (Dalecki et al., 2011), trials in which P50 click pairs were preceded by other auditory stimuli (in a 1000 ms pre-stimulus window) were excluded from analyses (leaving approximately 50 paired-click sets for analysis).

The percentage of trials rejected was less than 20% for all participants included in the final analyses. Data for each subject were averaged across trials and inspected to ensure that an adequate number of trials (a least 30) contributed to every waveform. Due

to the limited number of error trials available across participants (n = 11 participants with fewer than 10 error trials contributing to the ERN waveform), the ERN was not considered for the purposes of this study.

In conjunction with the literature regarding the general topography and form of each component, grand-averaged waveforms of all subjects informed the choice of electrode location and latency intervals for measurement. Mean amplitudes of difference waves were calculated for all components except P50 suppression, for which a S1-S2 difference was calculated using trough-to-peak amplitudes(Dalecki et al., 2011). P50 trough-to-peak amplitudes were calculated as the amplitude difference between the maximum peak in the window 40-70 ms and the preceding trough. Electrodes, latency windows, and isolation techniques used for measurement of each ERP component are summarized in Table 2. The final ERP profile consisted of eight measurements reflecting P50 suppression, Frequency MMN, Gap MMN, C1, vMMN, N2pc, P3, and LRP components.

Resting EEG. Due to a technical issue during recording, eyes-open data was not available for six participants. As a result, only eyes-closed activity was included in subsequent analyses. Spectral decomposition of a 60-second epoch of eyes-closed resting activity was accomplished using Welch's method for computing power spectral density. Frontal, central, and posterior regional power values in each band were calculated by averaging responses across eight frontal (FP1, FPz, FP2, F7, F3, Fz, F4, and F8), five central (T7, C3, Cz, C4, andT8), and eight posterior (P7, P3, Pz, P4, P8, O1, Oz, and O2) electrode sites. Log-transformed absolute power density values (log(X)) were calculated

over four conventional frequency ranges: Delta (1-3.5 Hz), Theta (4-7.5 Hz), Alpha (8-11.5 Hz), and Beta (12-29.5 Hz).

Statistical Analyses

Behavioral, demographic, and volumetric data were subjected to independent-samples t-tests to evaluate group differences. Fisher's exact tests (FET) were used to evaluate differences in the distribution of gender and medication prescription among diagnostic categories.

For spectral data, a Greenhouse-Geisser corrected 2 (diagnosis: aMCI, AD) x 3 (region: posterior, central, frontal) x 4 (bandwidth: Delta, Theta, Alpha, Beta) mixed analysis of variance (ANOVA) was conducted to evaluate differences between groups in regional power across frequency bands.Where significant main effects or interactions were observed, follow-up Bonferroni-corrected pairwise comparisons were used to evaluate individual effects. To evaluate group differences in ERP profiles, a one-way multivariate analysis of variance (MANOVA) was used. Follow-up independent samples t-tests were used to assess univariate differences between groups on each element of the profile, with an adjusted cutoff of $p = .006$ (marginal$p = .01$).

For both EEG and ERP profiles, discriminant analyses were conducted with diagnostic category (aMCI or AD) as the dichotomous dependent variable, and cross-validated, leave-one-out classification (in which individual cases are classified using a function derived from all other cases excluding the case under consideration) was used to evaluate predictive accuracy of the profiles. For EEG profiles, stepwise discriminant analysis was used as the number of variables (12) exceeded the number of participants in each group. Sensitivity to AD diagnosis was calculated as the proportion of patients with

AD successfully classified (relative to total number of patients with AD in the analysis), and specificity was calculated as the proportion of patients without AD who were successfully excluded (relative to total number of patients without AD). Fisher's exact tests were employed to evaluate the significance of classification results relative to the actual distribution of aMCI and AD diagnoses. An additional set of exploratory stepwise discriminant analyses were performed on spectral EEG and ERP profiles to identify which combinations of predictors most effectively discriminated between groups in this sample.

Pearson's correlation coefficients and stepwise regression analyses using either EEG or ERP measurements as prospective predictors were used to evaluate the relation between EEG/ERP profiles and existing neuropsychological (MoCA score) and neuroimaging data (hippocampal volume, inferior lateral ventricle volume, lateral ventricle volume, and hippocampal volume).

Results

Demographic and Behavioral Data

Behavioral results for the neurometric battery are summarized in Table 3. Initial analyses of behavioral data resulted in identification of seven participants with accuracy scores of less than 60%, suggesting failure to comprehend or comply with task instructions (AD: $n = 5$, aMCI: $n = 2$). The distribution of participants with poor performance did not significantly differ across diagnostic categories, *FET*, $p > .05$. Analyses were conducted in which participants with poor accuracy rates were both included and excluded, and in both cases, no significant differences in accuracy rates, reaction times (RTs) to correct trials, or RTs to incorrect trials were observed between

individuals with aMCI and individuals with AD. As certain elements of the ERP profile (e.g. N2pc, P3, LRP) are thought to index active attention and performance-related processes, participants with poor task comprehension were excluded from all analyses.[6]When comparisons were conducted between participants excluded for poor performance and the remaining 19 participants, significant differences were observed in years of education, $t(24) = 2.93$, $p = .009$, and the Orientation subscale of the MoCA, $t(24) = 2.81$, $p = .010$, such that excluded participants had fewer years of education and lower Orientation scores than participants who were included in the analyses.

Comparisons of demographic variables for the remaining 19 participants by diagnostic category are summarized in Table 1. Significant group differences were observed in total MoCA score, Naming, and Orientation subscales (such that lower scores were observed for patients with AD), as well as medication distribution (such that a greater proportion of participants with AD were being treated with donepezil/memantine at the time of the study).

For the 12 participants with available MRI data, volumetric information are summarized in Table 4. AD diagnosis was associated with greater lateral ventricle and inferior lateral ventricle volume, as well as lower hippocampal occupancy score. No significant difference in hippocampal volume was observed between participants with AD and aMCI in this sample.

[6]Although resting EEG is task-independent, participants were also excluded from spectral analyses for ease of comparison.

Resting EEG

Grand-averaged topographies of absolute power in each of the four frequency bands for each diagnostic category are presented in Figure 2. Mean regional power values for each group are presented in Table 5.

Group differences. When mixed ANOVAs were conducted with regional power values in each of four frequency bands as dependent variables, a significant interaction between region and diagnosis was observed, $F(2,34) = 4.82$, $p = .021$, with greater overall power over frontal and central regions in patients with AD.[7]

When regional power variables were entered into a stepwise discriminant analysis with diagnostic category as the dependent variable, only frontal theta power was entered into the model as a significant predictor of group membership, *Wilk's* $\lambda = 0.69$, $\chi^2(1) = 6.23$, $p = .013$, *Canonical Correlation* = .56. Leave-one-out cross-validated classification using frontal theta power yielded a success rate of 68% (13 out of 19 cases correctly classified), resulting in sensitivity and specificity rates of 67% and 70%, respectively. The proportion of participants correctly classified into original diagnostic categories using frontal theta power was non-significant, *FET*, $p > .05$.

Relation to neuropsychological and volumetric data. No significant correlations were observed between regional power values and MoCA score, andwhen regional power values in the four frequency bands of interest were entered into a stepwise regression with total MoCA score as the dependent variable, no variables were selected.

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[7] Interactions between region and bandwidth, $F(6,102) = 8.41$, $p < .001$ (driven by regional differences in alpha power, which was reduced at frontal relative to posterior and central regions), and a main effect of bandwidth, $F(3,51) = 31.73$, $p < .001$(such that beta power was significantly lower than power in the delta, theta, and alpha bands, and delta power was significantly greater than theta power) were also observed.

Additional analyses were conducted for a subset of 12 participants with available volumetric data to evaluate whether any combinations of EEG spectral variables would predict hippocampal volume, inferior lateral ventricle volume, lateral ventricle volume, and hippocampal occupancy ratio. In correlational analyses, a relation between frontal theta and lateral ventricle volume was observed, $r(12) = .60$, $p = .039$. Although no predictors in the EEG spectral profile met criteria for entry into equations for hippocampal volume, inferior lateral ventricle volume, or hippocampal occupancy score, frontal theta power was selected as a significant predictor of lateral ventricle volume,$\beta = .60$,$F(1,10) = 5.62$, $p = .039$, $R^2 = .36$.

ERP Profiles

Averagedraw and difference waveforms for each ERP component are presented by diagnostic category in Figures 3 and 4. Mean amplitude measurements for each component are summarized by group in Table 6. For a visualization of multidimensional ERP profiles by diagnostic category, see Figure 5.

Inspection of the data revealed one participant whose C1 and P3 amplitudes were extreme compared to the rest of the sample (greater than 3 standard deviations above the sample mean). A review of the participant's individual ERP waveforms revealed no anomalies, and no justification was apparent for exclusion. However, all subsequent analyses were conducted both including and excluding this participant. Note is made in cases where exclusion altered the pattern of results.

Group differences. ERP measurements for eight components (C1, N2pc, vMMN, P3, Frequency MMN, Gap MMN, P50 suppression, and LRP) were subjected to a multivariate ANOVA, which revealed statistically significant differences in the

neurometric profiles of older adults with aMCI and AD, *Wilk's* $\lambda = 0.21$, $F(8,10) = 4.72$, $p = .013$, $\eta^2 = .79$.[8] In follow-up, univariate comparisons, groups were differentiated predominantly by the amplitude of the LRP, $t(17) = 3.29$, $p = .004$.

ERP measurements were subsequently entered into a discriminant analysis to evaluate the utility of the profile for predicting group membership. The ERP profile significantly predicted diagnosis of aMCI or AD, *Wilk's* $\lambda = 0.21$, $\chi^2(8) = 20.32$, $p = .010$, *Canonical Correlation* = .89. LRP amplitude loaded most strongly onto the discriminant function, followed by P50 suppression, C1, and N2pc amplitudes. Leave-one-out cross-validated classification resulted in a success rate of 79%, with 15 out of 19 cases correctly classified (7 with aMCI and 8 with AD). Sensitivity and specificity rates for the ERP profile were 89% and 70%, respectively, resulting in a significant proportion of participants correctly classified,*FET*, $p = .020$.

Exploratory discriminant analyses. An exploratory stepwise discriminant analysis was conducted on the data to evaluate the combination of markers that provided the best prediction in this sample. This analysis was conducted with ERP markers alone, and with a second, omnibus discriminant analysis that included both ERP- and EEG-based variables.In both analyses, a subset of two components (LRP and P50 suppression) were selected that optimally predicted group membership, *Wilk's* $\lambda = 0.42$, $\chi^2(2) = 14.03$, $p = .001$, *Canonical Correlation* = .76. Success rates of 79% were achieved when cross-validated leave-one-out classification was applied, for a sensitivity rate of 78% and a specificity of 80%. Classification accuracy using these markers was significant, *FET*, $p = .023$.

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[8]Effects remained when age, education, hearing, and vision were incorporated as covariates in separate analyses.

In light of the apparent strength of the LRP as a predictor in each of these analyses, a final simple discriminant analysis was conducted to evaluate the sensitivity and specificity of the LRP alone. The LRP alone significantly predicted group membership, *Wilk's* $\lambda = 0.61$, $\chi^2(1) = 8.14$, $p = .004$, *Canonical Correlation* = .63, with a cross-validated classification accuracy of 79%. Sensitivity and specificity of the LRP for AD diagnosis were 78% and 80%, respectively, and significant classification accuracy was observed, *FET*, $p = .02$.

Relation to neuropsychological and volumetric data. Exploratory correlational and stepwise regression analyses were conducted to evaluate whether any combinations of ERP profile measurements would significantly predict total MoCA score. C1 amplitude was associated with MoCA score, $r(19) = -.51$, $p = .022$, and C1was entered into the regression equation as the only significant predictor, $\beta = -.52$, $F(1,17) = 6.35$, $p = .022$, $R^2 = .27$. However, this effect was not sustained when the participant with extreme C1 amplitude was excluded.

For the subset of participants with volumetric data, hippocampal volume was related to N2pc amplitude, $r(12) = .74$, $p = .006$, and LRP amplitude, $r(12) = .60$, $p = .037$; lateral ventricle volume was related to Gap MMN amplitude, $r(12) = .65$, $p = .023$, and LRP amplitude, $r(12) = -.77$, $p = .003$; inferior lateral ventricle volume was related to N2pc, $r(12) = -.66$, $p = .021$, and LRP amplitudes, $r(12) = -.62$, $p = .033$; and hippocampal occupancy ratio was related to N2pc, $r(12) = .68$, $p = .015$, and LRP amplitudes, $r(12) = .64$, $p = .026$.Scatter diagrams of significant correlations are presented in Figure 6.

When stepwise regression analyses were conducted to evaluate which predictors best accounted for variance in volume of medial temporal lobe structures (hippocampal volume, inferior lateral ventricle volume, lateral ventricle volume, and hippocampal occupancy ratio), LRP was selected as a predictor of lateral ventricle volume, $\beta = -.77$, $F(1,10) = 14.71$, $p = .003$, $R^2 = .60$; and N2pc was selected as a significant predictor of hippocampal volume, $\beta = .74$, $F(1,10) = 11.82$, $p = .006$, $R^2 = .54$, inferior lateral ventricle volume, $\beta = -.66$, $F(1,10) = 7.52$, $p = .021$, $R^2 = .43$, and hippocampal occupancy score, $\beta = .69$, $F(1,10) = 8.51$, $p = .015$, $R^2 = .46$.

Discussion

The primary aim of this study was to evaluate the utility of this tool and the resulting profile of metrics for use in clinical settings to detect changes in sensory, perceptual, or cognitive function associated with different levels of AD-related pathology. To assess the potential value of the design, it was first necessary to ascertain whether participants with potentially significant neurological impairments would be able to successfully complete the battery. Absent technical difficulties, the majority of participants (26 of 28) were comfortable completing the task. Of those who completed the task, the majority (19 of 26) exhibited good task comprehension, as indicated by above-chance accuracy levels. In addition, no significant differences in accuracy rates or reaction times were observed between individuals with AD or aMCI diagnoses, indicating comparable ability to complete the task across groups. Comprehension and completion rates support the potential candidacy of this task for use as a screening and research tool in clinical populations.

Sensitivity and Specificity of the ERP Profile

A second area of interest was whether ERP profiles derived from this battery would be sensitive to differences between participants with different levels of AD-related symptomology (as defined by diagnosis of aMCI or mild AD), as well as whether ERP metrics would be of comparable sensitivity to EEG neurometrics, or other existing markers of cognitive decline. For the purposes of this study, simple, established methods for assessing ERP and EEG data were used. For EEG data, analyses were constrained to absolute regional power in four primary frequency bands. For ERP data, analyses were constrained to differences in mean amplitudes of difference waves at single or paired electrode sites in windows within the bounds suggested by existing literature.

Discriminant analysis using ERP profiles resulted in significant differentiation between individuals with aMCI and mild AD, with a cross-validated sensitivity of 89%, a specificity of 70%, and greater-than-chance classification accuracy. In exploratory analyses that included both EEG and ERP predictors, two ERP variables (P50 suppression and LRP) were identified as optimally differentiating groups. The LRP, in particular, emerged as a strong predictor of diagnostic category, with an individual sensitivity of 78% and a specificity of 80% (more negative LRP amplitude being associated with AD diagnoses). The classification accuracy of the LRP alone contrasts with the single frontal theta predictor identified in the resting EEG profile, for which cross-validated classification accuracy was non-significant, and suggests that ERP measurements may have utility comparable to or exceeding resting EEG for detection and classification.

Relation to Neuropsychological and Volumetric Data

In addition to sensitivity and specificity of the ERP profile, the relation of EEG and ERP data to neuropsychological assessment and volumetric data was evaluated, with the expectation that a prospective ERP marker should relate to existing metrics in addition to predicting diagnosis. With respect to neuropsychological information, no relation between ERP or EEG markers and MoCA score, a common neuropsychological index of global cognitive function, was observed (given that the relation of C1 to MoCA was not sustained in the absence of an outlier). The MoCA is reported to have excellent sensitivity and specificity, but there is substantial overlap in the range of scores typically associated with patients with AD and those with aMCI (Nasreddine et al., 2005). Given this potential overlap, the lack of observable relation between ERP/EEG variables and MoCA score is not surprising in a small sample of patients with aMCI and mild AD. A more appropriate evaluation of the relation of MoCA score to ERP markers could be accomplished in a sample contrasting cognitively normal participants with those with aMCI and AD.

As structural MRI data were available only for a subsample of participants, the results of stepwise analyses of volumetric data are interpreted with caution. Given the comparatively large number of variables in the EEG (12) and ERP (8) profiles relative to the number of participants (12), over-fitting and influence of outliers were significant concerns, and interpretation of effects of individual predictors is largely constrained to those that varied consistently across multiple domains of analysis.

In the EEG profile, frontal theta power was selected as a significant predictor of lateral ventricle volume, with increases in frontal theta power being associated with

increases in lateral ventricle volume. This observation is compatible with the selection of frontal theta to differentiate between AD and aMCI in stepwise discriminant analyses, where greater frontal theta power was associated with increased likelihood of AD diagnosis. Increased power in the theta band has been observed in the earliest stages of AD (Coben, Danziger, & Berg, 1983; Coben, Danziger, & Storandt, 1985), and has been linked to decreases in hippocampal volume associated with increased severity of the disease (Grunwald et al., 2001; Grunwald, Hensel, Wolf, Weiss, & Gertz, 2007). In these studies, additional structures were not assessed. The observation of a relation between frontal theta and lateral ventricle volume in the absence of any relation between theta power and hippocampal volume in our sample might suggest a more general relationship between resting theta power and medial temporal atrophy.

For ERP data, the relation between N2pc and hippocampal volume, inferior lateral ventricle volume, and hippocampal occupancy ratio appears largely due to a single influential participant (Figure 6),[9] and the influence of this case renders interpretation of these results problematic. There is no reason to suspect the data of the outlying individual might be contaminated, and it is possible that a sample including participants with a greater range of temporal atrophy would confirm the N2pc as a predictor (it is equally possible that thisfinding is anomalous). One advantage of this neurometric batteryis that issues like interpretation of the relation of N2pc to medial temporal atrophy may be easily evaluated in follow-up studies in conjunction with other analyses, such that few resources are wasted through devotion exclusively to a spurious effect.

[9]When this outlier was excluded from the data, the N2pc was no longer a significant predictor, and instead frequency MMN, P3, LRP, and vMMN were identified as volumetric predictors in stepwise regression analyses.

As with the N2pc, LRP data were correlated with volumetric measurements. The relation between LRP amplitude and volumetric data varied predictably, such that increases in LRP amplitude (more negative difference waves) were associated with lower hippocampal volume, greater inferior lateral ventricle volume, and lower hippocampal occupancy ratio. LRP amplitude was additionally identified as a significant predictor of lateral ventricle volume, such that increases in LRP amplitude were associated with increases in lateral ventricle volume. The direction of these observations is consistent with the observed amplified LRP in patients with AD relative to those with aMCI.

The LRP Component and AD

The LRP is thought to index central response activation/preparation in the primary motor cortex, and amplification of the LRP has been suggested to indicate greater levels of response activation(Smulders & Miller, 2012). There are a number of possible explanations for the observed differences in LRP amplitude between groups in this task, including task-related, cognitive/behavioral, and anatomical factors. Task-related factors that might impact the LRP include presence of horizontal artifacts due to lateralization of targets, consistent lateralized activity due to looking at an effector immediately prior to response, or differential distributions of key-target assignment between groups(Smulders & Miller, 2012). Effects of horizontal artifacts in the data should be negligible and similar across participants. Obvious horizontal artifacts were corrected in the data during processing using ICA, and as target location was randomized across trials, residual horizontal ocular artifacts are expected to cancel in the averaged waveforms.

Contralateral activity resulting from participants looking at an effector immediately prior to responding could also contaminate the LRP waveform. If systematic group differences in participants looking at an effector prior to response were present, a corresponding increase in reaction time might be expected, butno difference in reaction times was observed between groups. Additional systematic variation in the LRP might be observed if common/rare key-target assignments were not truly random across groups. Analyses of the distribution of response-key assignments revealed no significant group differences, however, *FET,* $p = .130$.

Effects related to stimulus-response compatibility and lateralization of attention relative to the target (as indexed by the N2pc component) might also be expected to interact with the LRP, and these effects could differ substantially between patient groups. Contamination due to the N2pc might be expected to result in greater negativity of the LRP waveform on trials spatially compatible with the response (relative to spatially incompatible trials), and differential distribution of accuracy between groups for compatible and incompatible trials could impact LRP amplitude. For example, if participants in the AD group responded correctly to a greater proportion of compatible trials than participants in the aMCI group, the amplified LRP in AD might simply reflect the effects of compatibility on accuracy in AD patients. Although analyses of behavioral data confirmed the occurrence of increased proportions of correct compatible responses relative to correct incompatible responses across participants, $F(1,17) = 4.80$, $p = .043$, no interaction was observed between diagnosis and proportion of compatible relative to incompatible responses. In addition, when controlling for individual variation in the effects of compatibility, the relation between diagnostic category and LRP remained,

$F(1,16) = 9.77$, $p = .007$. When LRP amplitudes following compatible and incompatible trials were compared across groups, a main effect of compatibility was observed such that participants in both groups exhibited amplified responses on compatible trials, $F(1,17) = 4.78$, $p = .043$. No interaction between diagnosisand compatibility was observed, however.

The relation of LRP amplitude to volumetric data supports an anatomical explanation for group differences, in which amplification of the LRP may be due to differences in underlying neuroanatomy at different stages of AD. As EEG activity is the result of summated firing across cortical regions, dramatic changes in structural volume and/orsynaptic integrity may shift or alter firing patterns such that certain values are atypically attenuated in some areas of the cortex and amplified in others. Additionally, neural compensatory effects may result in increases in brain activity in patients with greater levels of neurodegeneration(Elman et al., 2014), and it is possible that similar damage-related compensatory mechanisms result in altered firing patterns during response preparation. Age-related differences have been also reported in LRP amplitude (Roggeveen, Prime, & Ward, 2007), butdifferences in LRP between groups remained significant when age was included as a covariate, $F(1,16) = 7.67$, $p = .014$.

Although there are few reports of LRP amplitude changes in the context of MCI and AD,attenuations of LRP amplitude in Simon tasks have been observed in MCI relative to healthy aging (Cespón, Galdo-Álvarez, & Díaz, 2013; Cespón, Galdo-Álvarez, Pereiro, & Díaz, 2015). The observed amplification of the LRP in patients with AD diagnoses in the current study suggests either a differential, U-shaped pattern of reduction and amplification over the course of the disease, or that variations in task parameters may

substantially alter the behavior of the LRP as a biomarker of cognitive decline. U-shaped curves in ERP behavior have been observed for other ERP components in comparisons of healthy controls, patients with aMCI, and patients with AD, and may reflect different patterns of neurodegeneration associated with different stages of the disease (e.g. Golob, Irimajiri, & Starr, 2007). As the LRP shows prospective utility as a biomarker at multiple stages of disease progression, additional investigation of the directionality and task-specificity of these effects is warranted.

General Conclusions

Assessment of the utility of this profile suggests that (a) the task is feasible for implementation in clinical settings, (b) ERP profiles derived from this task can be used todifferentiate between individuals with different diagnoses, and (c) ERP measurements derived from this task can be sensitive to differences associated with underlying pathophysiological changes related to AD. Although classification accuracies of the profiles evaluated here did not reach the same level as established neuropsychological assessments such as the MoCA (sensitivity ~90%, specificity ~87%; Nasreddine et al., 2005), or combined CSF biomarkers (sensitivity ~95%, specificity ~85%; Humpel, 2011), they do compare favorably to existing reports of ERP-based classifiers developed in similar samples (Chapman et al., 2007, 2011, 2013).[10]

The sensitivity of ERP profiles generated using this task to differences between patients at different levels of decline is encouraging, and suggests that with further evaluation, profiles derived using the tool might be used to discriminate between groups

[10]Note that we evaluate differences between levels of AD pathology, which differs from evaluation of differences between healthy controls and those with AD or aMCI diagnoses. As such, our sensitivity rates are more reflective of classification accuracy than sensitivity with respect to the general population.

with accuracy comparable to standard neuropsychological and biomarker-based assessments. Additional steps to improve the utility of these profiles include testing in samples of healthy older adults as well as patients with aMCI and AD, and development of standardized, a priori filtering and data selection algorithms that limit subjective assessment of ERP data and utilize the full range of information available (as in principal component analysis, e.g.). In addition, acquisition of data from large-N samples would afford opportunitiesto evaluate the sensitivity and predictive accuracy of the profile with less risk of over-fitting the data; to more effectively train classifiers;and to apply clustering algorithms in order to identify sub-groups of individuals varying on latent dimensions.

Additional utility of this profile is derived from its pragmatic and efficient design, which allows not only identification of expected biomarkers, but also the opportunity to assess relative utility of different combinations of markers, and to identify prospective markers in unexpected areas. This type of EEG recording has the advantages of being noninvasive, brief, and relatively inexpensive, in addition to providing a wealth of both resting state and event-related information. A full analysis of all possible variables that could be extracted from this profile is beyond the scope of this paper, but additional metrics that could be incorporated include resting relative power, regional asymmetry, coherence, complexity, and peak frequency, in addition to latency measurements, use of analysis techniques that incorporate all electrodes and time points, and evaluation of event-related oscillatory activity.

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Table 1

Comparison of demographic variables by diagnostic category

	aMCI (n = 10)	AD (n = 9)	
	M (*SD*)	*M* (*SD*)	*t*(17) or *FET*
Age (years)	75.90 (10.14)	83.11 (4.51)	-1.96
Education (years)	15.10 (2.60)	13.89 (2.57)	1.02
AD8 (__/8)	4.70 (2.50)	6.00 (1.73)	-1.30
MoCA (__/30)*	21.30 (2.21)	18.11 (3.86)	2.24*
Visuospatial/Executive (_/5)	3.60 (0.97)	3.00 (1.32)	1.14
Naming (_/3)*	2.80 (0.42)	2.22 (0.44)	2.92*
Attention (_/5)	5.00 (1.33)	4.33 (1.12)	1.17
Language (_/3)	1.90 (0.88)	1.78 (1.09)	0.27
Abstraction (_/2)	1.90 (0.32)	1.89 (0.33)	0.08
Delayed Recall (_/5)	0.60 (1.07)	0.33 (0.71)	0.63
Orientation (_/6)*	5.50 (0.71)	4.44 (1.13)	2.37*
Hearing (__/40)	5.00 (5.01)	8.00 (8.77)	-0.93
Vision (20/__)	32.50 (14.19)	32.78 (10.04)	-0.05
Donepezil (*n*)**	0	6	*FET***
Gender (*n* female)	8	5	*FET*

Note. * denotes $p < .05$; ** denotes $p < .01$. Fisher's exact tests (FET) were used to test gender and medication distributions.

Table 2

Electrodes and latency windows for measurement of ERP components

ERP	Electrode(s)	Latencies (ms)	Isolation technique
P50	Fz	40 to 70	S1-S2 Difference
MMN_{GAP}	Fz	150 to 250	Difference wave (deviant – standard)
MMN_{FREQ}	Fz	175 to 225	Difference wave (deviant – standard)
C1	Pz	50 to 100	Difference wave (lower – upper)
vMMN	Oz	180 to 280	Difference wave (deviant – standard)
N2pc	P7/P8	250 to 350	Difference wave (contralateral – ipsilateral)
P3	Pz	450 to 750	Difference wave (deviant – standard)
LRP	C3/C4	-150 to -50	Difference wave (contralateral – ipsilateral)

Note. Latencies are measured relative to the time-locked event of interest, and negative values indicate measurements in the period prior to the time-locked event. For LRP and N2pc measurements, responses to left/right stimuli and responses were extracted and recombined to create contralateral and ipsilateral waveforms.

Table 3

Comparison of behavioral results for participants with aMCI and AD

	aMCI (n = 10)	AD (n = 9)	
	M (*SD*)	*M* (*SD*)	*t*(24)
Accuracy (% correct)	0.81 (0.28)	0.72 (0.25)	0.84
Correct RT (seconds)	0.44 (0.13)	0.55 (0.16)	-1.90
Incorrect RT (seconds)	0.38 (0.11)	0.53 (0.26)	-2.01

Note. All $p > .05$.

Table 4

Volumetric data for the MRI subsample, grouped by diagnostic category.

	aMCI (n = 8)	AD (n = 4)	
	M (*SD*)	*M* (*SD*)	*t*(10)
Hippocampal Volume (cm^3)	7.19 (0.77)	6.18 (0.97)	2.00
Inferior Lateral Ventricle Volume (cm^3)	2.62 (1.29)	4.95 (1.96)	-2.50*
Lateral Ventricle Volume (cm^3)***	35.75 (14.63)	88.48 (15.76)	-5.75***
Hippocampal Occupancy score	0.74 (0.10)	0.56 (0.13)	2.59*

Note. * denotes $p < .05$; *** denotes $p < .001$. Hippocampal occupancy was calculated as the ratio of hippocampal volume to the sum of hippocampal and inferior lateral ventricle volumes.

Table 5

Log-transformed regional power values in each frequency band by diagnostic category

		aMCI (n = 10)	AD (n = 9)
		M (*SD*)	*M* (*SD*)
Delta	Posterior	0.49 (0.51)	0.55 (0.33)
	Central	0.31 (0.48)	0.65 (0.32)
	Frontal	0.36 (0.37)	0.72 (0.39)
Theta	Posterior	0.15 (0.54)	0.40 (0.47)
	Central	-0.05 (0.51)	0.44 (0.42)
	Frontal	-0.09 (0.43)	0.44 (0.39)
Alpha	Posterior	0.40 (0.63)	0.45 (0.59)
	Central	0.16 (0.50)	0.52 (0.50)
	Frontal	0.04 (0.38)	0.39 (0.42)
Beta	Posterior	-0.20 (0.40)	-0.32 (0.41)
	Central	-0.39 (0.35)	-0.07 (1.35)
	Frontal	-0.31 (0.41)	-0.10 (0.42)

Note. Standard deviations are listed parenthetically following means.

Table 6

Mean amplitudes for each ERP component by diagnostic category

	aMCI (n = 10)	AD (n = 9)
	M (*SD*)	*M* (*SD*)
P50 S1-S2 Difference	-0.05 (0.74)	0.78 (1.03)
Frequency MMN	-0.12 (1.48)	-0.54 (1.50)
Gap MMN	-0.09 (0.95)	-0.35 (1.41)
C1	1.99 (2.19)	3.83 (3.84)
vMMN	-0.47 (0.88)	-0.82 (1.12)
N2pc	-0.27 (0.31)	-0.48 (0.65)
P3	0.36 (0.59)	0.55 (2.32)
LRP	-1.04 (1.02)	-2.63 (1.08)

Note. All units are μV.

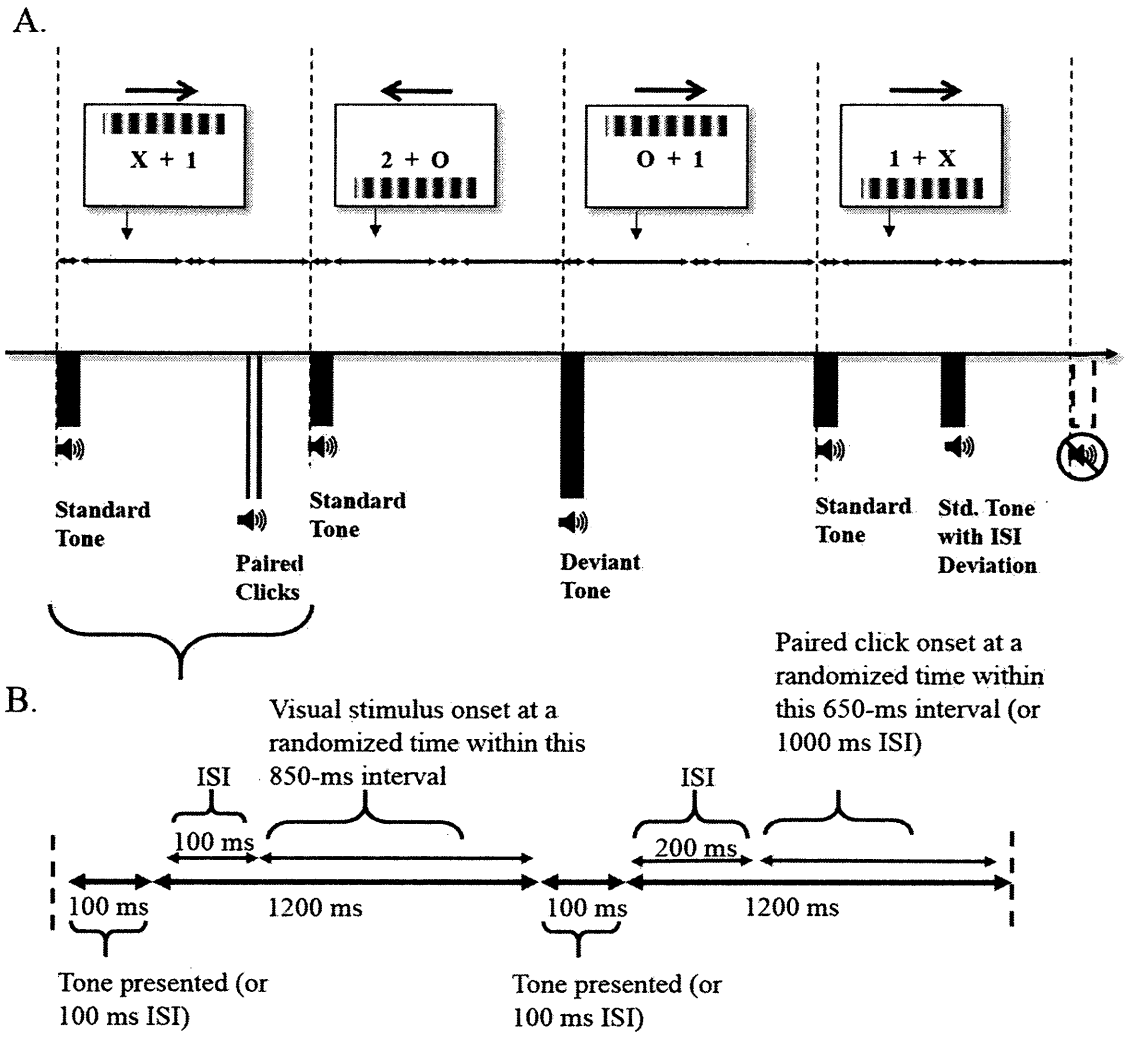

Figure 1. (a) Sample schematic of four trials in which target stimuli were numbers '1' and '2.' Arrows are used to indicate the direction of apparent sine grating motion. Each trial consisted of one visual event and up to two auditory events. (b) Timing of a single trial. Trial duration was fixed at 2600 ms, and both type and presence/absence of auditory stimuli varied between trials.

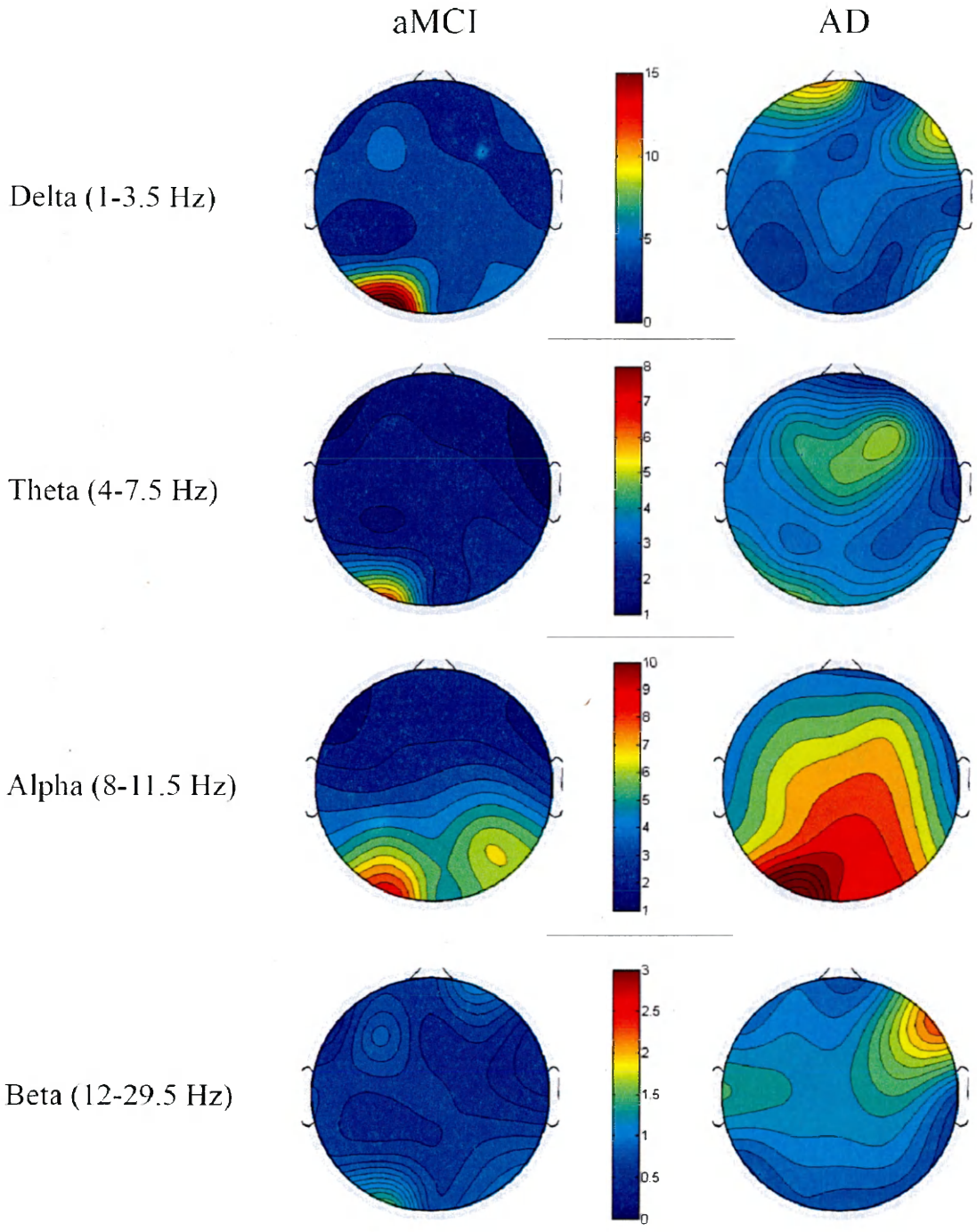

Figure 2. Topographies of absolute untransformed power by frequency band, averaged across participants for each diagnostic category.

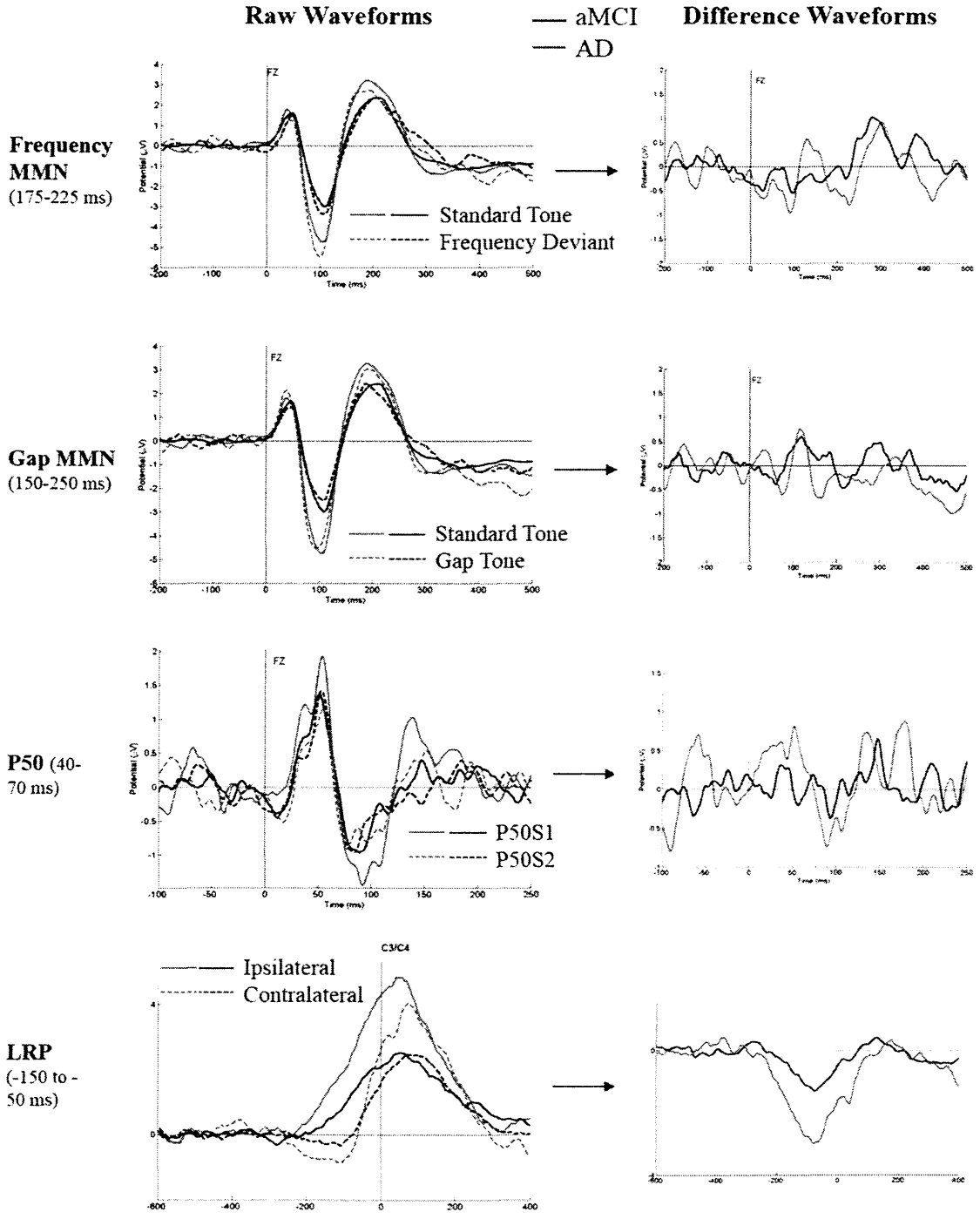

Figure 3. Raw and difference waveforms for Frequency MMN, Gap MMN, P50 suppression, and LRP by diagnostic category.

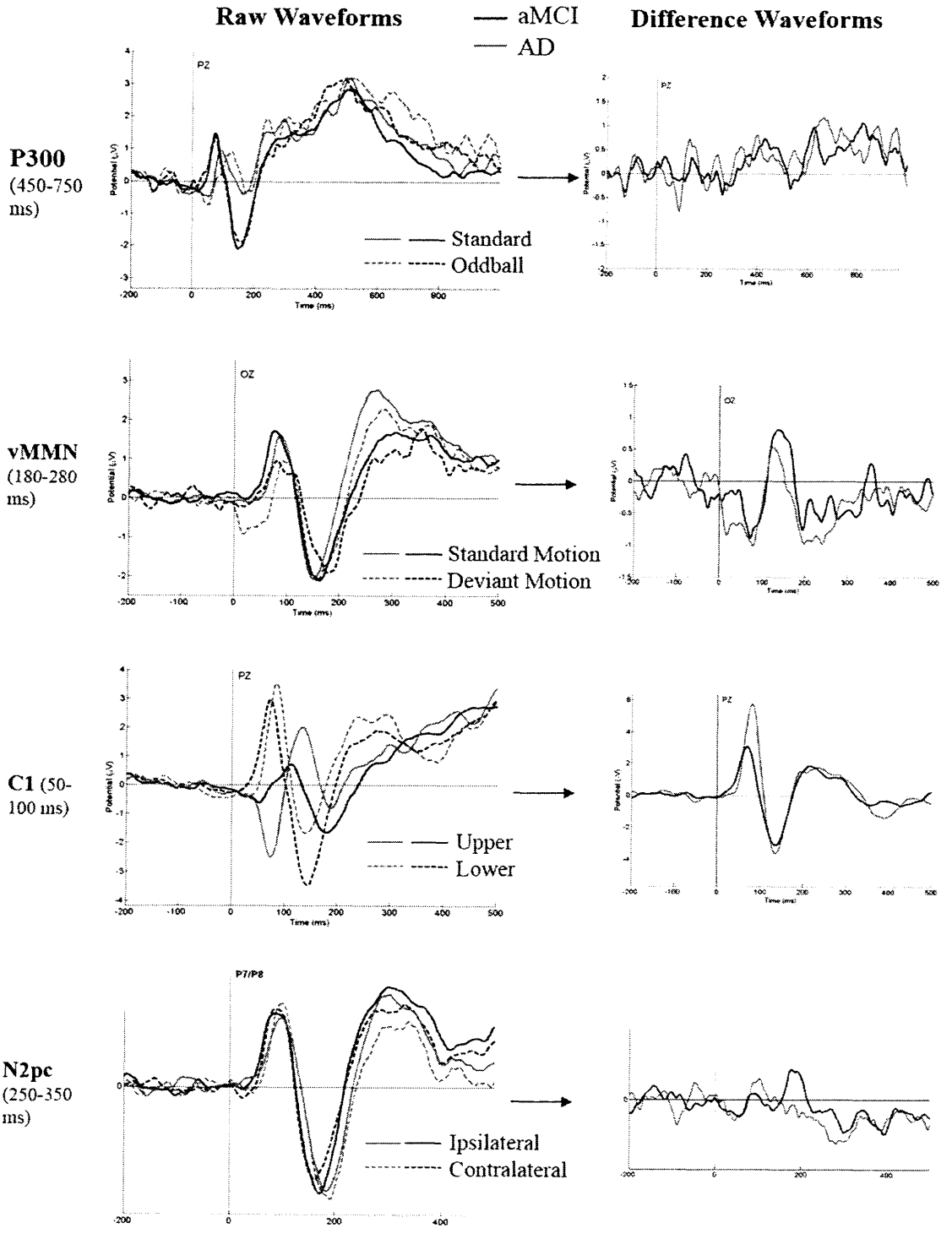

Figure 4. Raw and difference waveforms for visual ERP components (P3, vMMN, C1, N2pc) by diagnostic category.

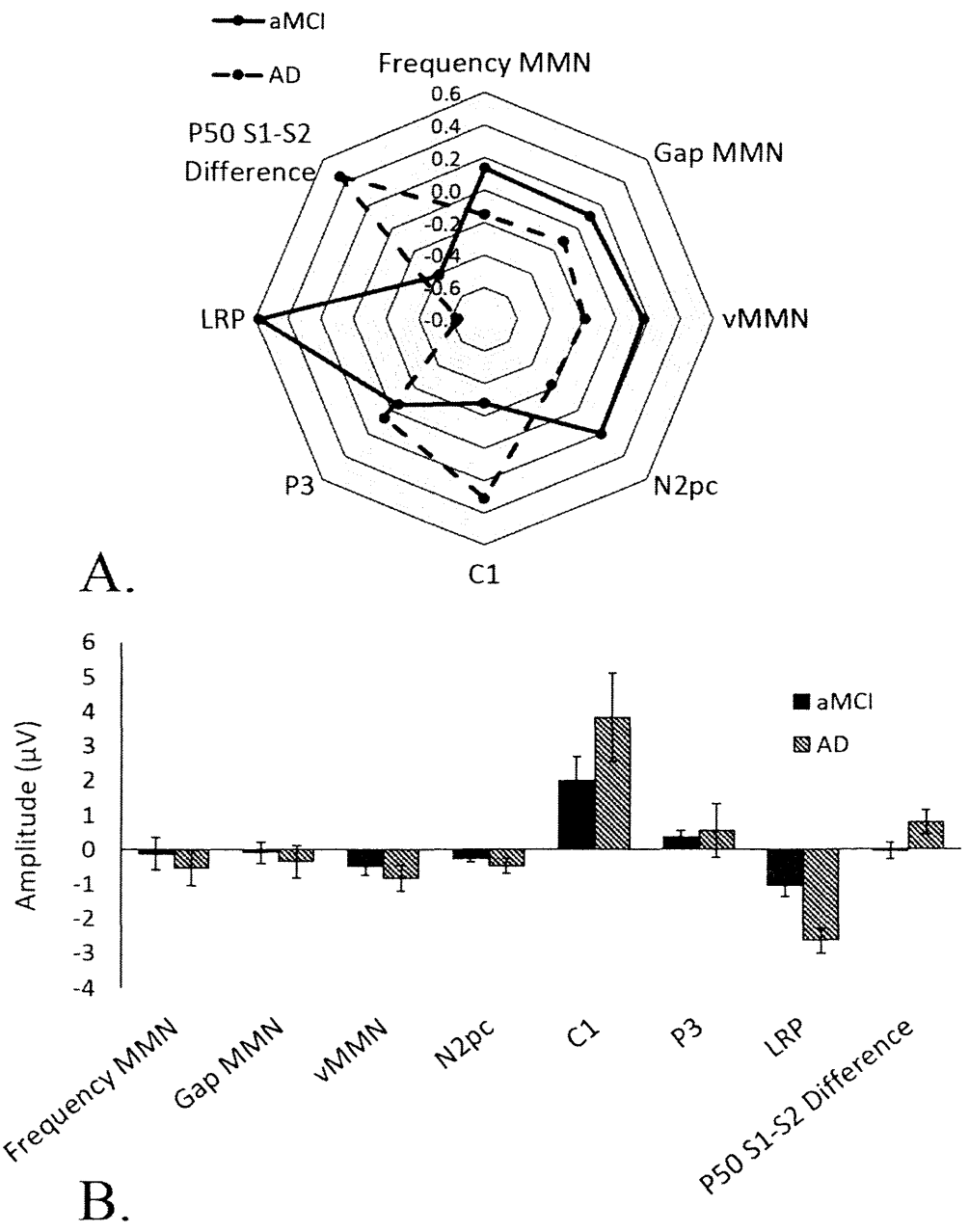

Figure 5. (A) Radial plot of standardized ERP profile measurements for AD and aMCI. (B) Mean amplitudes for each ERP component by diagnostic category, with standard error.

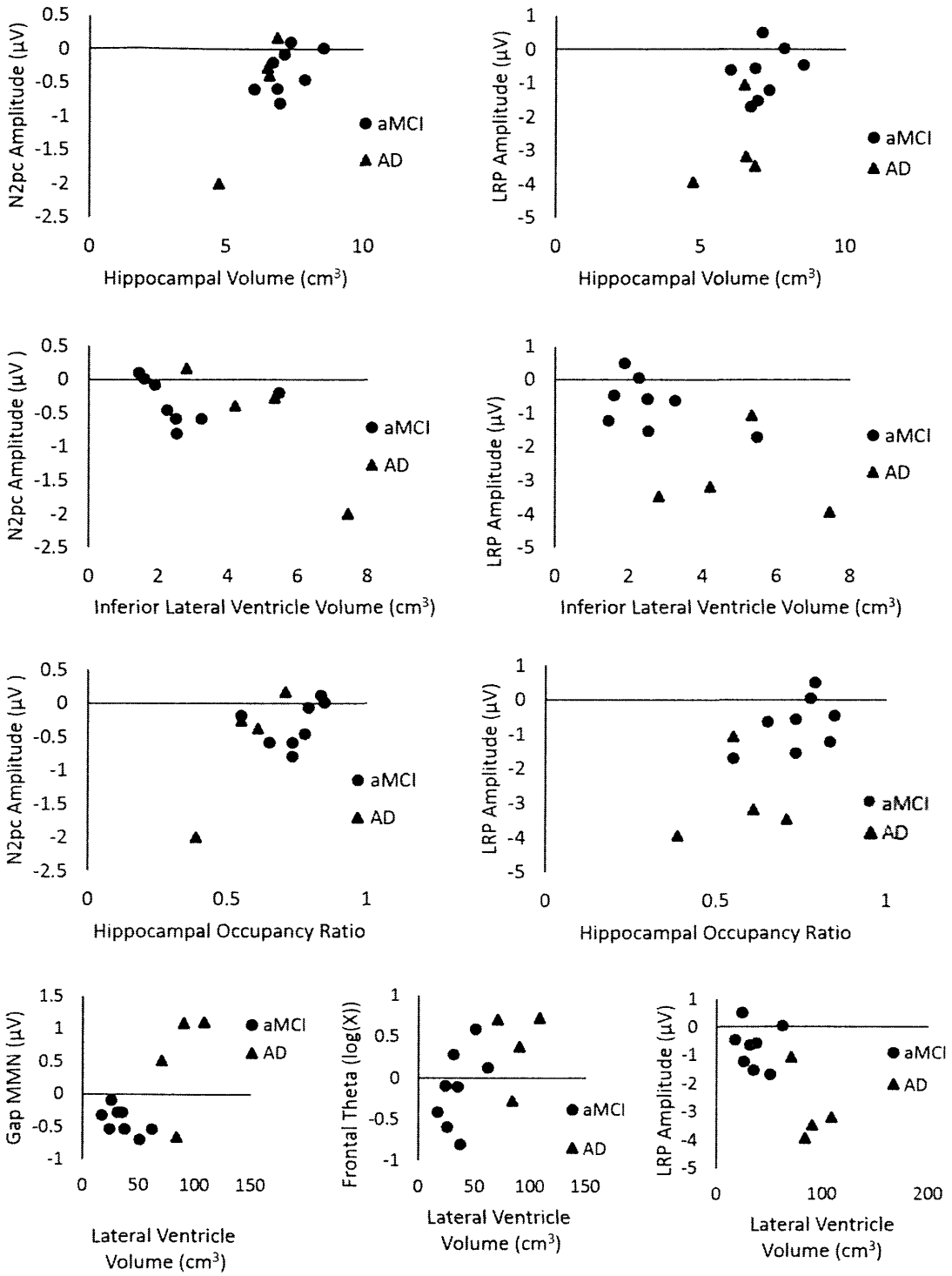

Figure 6. Scatter diagrams of significant relationships between EEG/ERP and volumetric variables.