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Event-related potentials during sustained attention and memory tasks: Utility as biomarkers for mild cognitive impairment

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Abstract

Objective: The objective of the study is to validate attention and memory tasks that elicit event-related potentials (ERPs) for utility as sensitive biomarkers for early dementia.

Methods: A 3-choice vigilance task designed to evaluate sustained attention and standard image recognition memory task designed to evaluate attention, encoding, and image recognition memory were administered with concurrent electroencephalography acquisition to elicit ERPs in mild cognitive impairment (MCI) and healthy cohorts. ERPs were averaged, and mean or max amplitude of components was measured and compared between and within groups.

Results: There was significant suppression of the amplitude of the late positive potential in the MCI group compared with the healthy controls during 3-choice vigilance task, predominantly over occipital and right temporal-parietal region, and standard image recognition memory task over all regions. During standard image recognition memory task, diminished performance showed strong correlation with electroencephalography measurements. The old/new effects observed in the healthy controls cohort correlated with performance and were lost in MCI.

Conclusions: ERPs obtained during cognitive tasks may provide a powerful tool for assessing MCI and have strong potential as sensitive and robust biomarkers for tracking disease progression and evaluating response to investigative therapeutics.

Keywords: Mild cognitive impairment; Neurophysiology; Electroencephalography; Event-related potential; Biomarker

1. Introduction

Alzheimer's disease (AD) and other dementias can be particularly difficult to distinguish in the early stages, when cognitive and/or motor impairments are subtle and often subclinical in presentation although critically important differences exist in the underlying pathophysiological processes of these diseases [1]. Early characterization is critical to initiate effective interventions, particularly treatments with purported "disease-modifying" effects [2]. Investigators of novel treatment options for AD and other neurodegenerative diseases urgently need sensitive, reliable, cost-effective, noninvasive tools to quantify cognitive deficits associated with neurodegeneration, preferably in the earliest detectable stages of the underlying pathophysiological process. Neurophysiological metrics including quantitative electroencephalography (EEG) and event-related potentials reliably measure the neural circuits associated with cognitive processes and may provide sensitive metrics for early diagnosis, tracking disease progression, and assessing efficacy of novel interventions.

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Event-related potentials (ERPs) are reflections of summated postsynaptic inhibitory and excitatory membrane potentials primarily generated by cortical pyramidal cells. Characteristic time-locked ERP waveforms are elicited in response to sensory, motor, and cognitive events [3]. Components of the waveforms can be used to differentiate cognitive conditions, making ERP methods ideal for quantifying cognitive decline in patients with dementia [4,5]. ERPs track the flow of information from sensory processing and analysis to response. Early components (50–200 ms poststimulus) reflect sensory processing of the characteristics of the stimuli but can be influenced to some extent by arousal and attention [6,7]. The late ERP components (P300, N400, P600, and late positive potential [LPP]) reflect feature evaluation, memory matching, and processing speed [5,8]. Multiple reports suggest that abnormal amplitude and latency of the LPP are associated with cognitive decline [9–11]. The LPP is believed to reflect memory encoding and retrieval with possible sources located in the parahippocampal gyrus, medial temporal lobe, and posterior cingulate regions known to be affected during the progression of dementia [12].

There exists a strong foundation suggesting the utility of ERPs as quantitative biomarkers of cognitive processes [4,5,9–11,13–15]. ERPs reveal abnormal neuronal activity in AD beginning in the very early stages of the disease [16]. Word recognition–elicited ERPs show promise as biomarkers of disease progression and subsequent conversion to dementia in individuals with mild cognitive impairment (MCI) [10,11]. During memory tasks, activation of the LPP during target trials compared with nontarget trials is indicative of an old/new effect that reflects memory activation [17]. Thus, the target trials typically have an increased LPP compared with nontarget that is predominate over the parietal region [18]. In MCI patients, ERPs elicited in response to images had diminished old/new effects in MCI patients versus healthy controls [19]. Using this image recognition paradigm, ERPs acquired from presymptomatic carriers of the genetic mutations in presenilin-1 showed significant changes in ERP patterns years before the onset of symptoms [20].

The introduction of novel therapies for AD, MCI, and Parkinson's disease dementia will be more efficient if sensitive biomarkers can be identified for early diagnoses and be suitable for frequent repetition to assess disease progression. Amyloid positron emission tomography imaging is available to quantify the accumulation of β-amyloid known to be associated with AD pathology, but these measurements are made with limited frequency due to the limited access, expense, and cumulative radiation dose. ERPs may provide convenient inexpensive, noninvasive neurophysiological biomarker for early detection of dementia pathology. ERP methods could provide sensitive biomarkers independently, or alternatively, be used as a low-cost accessible prescreening procedure to identify individuals likely to be positive for a secondary, more costly and invasive imaging or other biomarker. Several studies suggest that ERPs are sensitive to the effects of approved pharmacological treatments for MCI and AD; ERP measures reliably reflect improvements in cognition following administration of cholinesterase inhibitors [21] and the selective N-methyl-D-aspartate antagonist memantine [22].

The present study compared a group of patients diagnosed with MCI to age-matched healthy controls (HCs) using tasks designed to activate the neural circuitry underlying the cognitive processes associated with sustained attention, visual recognition memory, and working memory. Patients with MCI are particularly interesting as potential targets for early intervention as MCI is often a transitional state between normal aging and dementia. However, although many patients with MCI progress rapidly to dementia, the rate of decline is highly variable, and a significant number remains stable or even return to age-appropriate levels of cognitive capabilities [23].

The participants were administered an ERP test battery with concurrently recorded EEG (Advanced Brain Monitoring, Carlsbad, CA) consisting of a 3-choice vigilance task (3CVT) [24,25] designed to evaluate sustained attention and standard image recognition memory task (SIR) designed to evaluate attention, encoding, and image recognition memory. In the SIR, images were chosen as stimuli to distinguish short term from semantic memory loss and extend previous results of image recognition ERP effects [19,20]. The sustained attention and working memory tasks are designed to assess neurocognitive functions that may be compromised as a result of disease, drugs, or behavior (e.g., sleep loss). The combination of EEG and performance metrics [26–31] is highly sensitive and specific in quantifying daytime drowsiness (associated either with sleep deprivation in healthy participants [29,31,32] or in sleep disordered patients), predicting susceptibility to sleep deprivation [32], and assessing neurocognitive deficits in patients with sleep disorders and benzodiazepine-related driving impairment [31–33]. The present study extends these results to a MCI cohort to evaluate early, mild dementia. The objective of the study is to validate the ERP tasks as sensitive biomarkers for early dementia with potential utility as a pharmacodynamic end point in assessment of investigational disease-modifying therapeutics. The investigators hypothesized that patients with MCI will show suppressed LPP for each of the tasks, with more significant suppression in the memory recognition task.

2. Methods

2.1. Participants

Thirty-five individuals (Table 1) were enrolled in this study through the Brain Aging and Dementia Laboratory at Massachusetts General Hospital. Participants were referred for the study through the Massachusetts General