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Electrophysiological Biomarkers

A clinical trial to validate event-related potential markers of Alzheimer's disease in outpatient settings

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Abstract

Introduction: We investigated whether event-related potentials (ERP) collected in outpatient settings and analyzed with standardized methods can provide a sensitive and reliable measure of the cognitive deficits associated with early Alzheimer's disease (AD).
Methods: A total of 103 subjects with probable mild AD and 101 healthy controls were recruited at seven clinical study sites. Subjects were tested using an auditory oddball ERP paradigm.
Results: Subjects with mild AD showed lower amplitude and increased latency for ERP features associated with attention, working memory, and executive function. These subjects also had decreased accuracy and longer reaction time in the target detection task associated with the ERP test.
Discussion: Analysis of ERP data showed significant changes in subjects with mild AD that are consistent with the cognitive deficits found in this population. The use of an integrated hardware/software system for data acquisition and automated data analysis methods make administration of ERP tests practical in outpatient settings.

Keywords: Multicenter clinical trial; Event-related potentials; Oddball paradigm; Early stage Alzheimer's disease; Outpatient settings; Automated ERP data analysis

1. Background

Despite the emergence of putative biomarkers for Alzheimer's disease (AD) [1], clinical diagnostic accuracy is suboptimal [2]. A sensitive and reliable physiological measure of the cognitive deficits associated with AD could provide insight in the cognitive physiology of the disease, and help with diagnosis, and assessment of severity and progression.

Event-related potentials (ERP) reflect well-characterized brain responses to sensory, motor, and cognitive events [3]. As such, ERP methods are well suited to detect and quantify the cognitive deficits associated with AD [4]. ERP have been found to be altered in AD beginning in the very early stages of the disease. ERP tests on young presymptomatic individuals who carry mutations in the presenilin-1, and amyloid precursor protein genes show significant changes in ERP patterns years before the onset of behavioral symptoms and the development of AD [5,6]. ERP have shown potential utility as biomarkers of disease progression and

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subsequent conversion to dementia in individuals with mild cognitive impairment (MCI). ERP responses to auditory stimuli contain discriminative information that predicts which MCI patients are likely to progress to AD [7], and patients with amnestic MCI that are at high risk of conversion to AD have abnormal ERP during a word repetition task [8]. ERP have also been shown to reliably track the cognitive decline associated with AD progression. ERP markers of cognitive function are increasingly altered in longitudinal studies on MCI and AD patients [9,10]. Finally, ERP are sensitive to the effects of cognitive enhancers currently used for the treatment of AD. ERP measures are reliable instruments for the assessment of the cognitive response to cholinesterase inhibitors such as donepezil, while the effects of the selective N-methyl-D-aspartate (NMDA) antagonist memantine on ERP correlate with changes in mini-mental state examination (MMSE) score [11–13].

Although the potential of ERP as a sensitive and reliable cognitive biomarker for AD has been known for a long time (for review, see [14–16]), the promise of this technique has not been yet fully realized through wide adoption of ERP in clinical use. Primary reasons have been the lack of standardization of ERP acquisition and data analysis techniques, and the impracticality of conducting ERP tests in clinical environments on actual patients. Recent advances in electronics and analysis algorithms have made it possible to administer ERP tests in a practical manner. There is now a need for large population-based studies that can confirm the usefulness of ERP as cognitive biomarkers for AD outside the laboratory [6].

In our multicenter clinical study, we investigated whether ERP collected in an outpatient setting and analyzed with automated, standardized methods can achieve results equivalent to those reported from academic laboratories and provide a sensitive and reliable measure of the cognitive deficits associated with early AD.

2. Materials and methods

2.1. Study participants

A total of 103 subjects with probable mild AD and 101 healthy controls (HC) aged between 60 and 90 years were recruited at seven clinical study sites. The study (ClinicalTrials.gov number NCT00938665) was approved by institutional review boards for each site, and a written informed consent was obtained from each study participant.

2.2. Subjects screening

All study subjects received a thorough medical history and neurologic examination. General inclusion criteria for the study included a modified Hachinski score $\leq$4 and a geriatric depression scale (GDS) short form score $\leq$5. Exclusion criteria were the use of antidepressants other than selective serotonin uptake inhibitors, major psychiatric disorders, and clinically significant neurologic diseases other than AD. Subjects taking sedatives and/or memory dietary supplements were asked to suspend them for the 72 hours before screening and testing.

The diagnosis of probable AD was made on the basis of the National Institute of Neurological and Communication Disorders and the Stroke-Alzheimer's Disease and Related Disorders Association criteria [17]. The inclusion criteria for the AD cohort were designed to recruit subjects in the early stages of the disease and encompassed an MMSE score between 21 and 26, a clinical dementia rating (CDR) score of 0.5, 1, or 2, and an education adjusted score on the delayed recall of the Wechsler logical memory II subscale of $\leq$3 for 0–7 years of education, $\leq$5 for 8–15 years of education, and $\leq$9 for 16 or more years of education.

Inclusion criteria for the HC cohort were an MMSE score of 27 and above, a CDR score of 0, and an education adjusted score on the delayed recall of the Wechsler logical memory II subscale of $\geq$4 for 0–7 years of education, $\geq$6 for 8–15 years of education, and $\geq$10 for 16 or more years of education.

2.3. Experimental paradigm

Subjects who met inclusion criteria at screening were tested using a three-stimulus oddball paradigm (for review, see [18,19]).

Stimuli comprised of standard tones (1000 Hz), target tones (2000 Hz), and unexpected distractor tones (white noise) that were played with probabilities of .75, .15, and .10. Tones were presented in pseudorandom order, so that target and distractor tones were never presented sequentially [20]. Subjects were instructed to respond to the target stimuli by pressing a button with their dominant hand. For each test, between 300 and 400 stimuli were presented binaurally through insert ear phones at 70-dB volume. The tone duration for each stimulus was 100 ms with rise and fall times of 10 ms. The interstimulus interval was randomized between 1.5 and 2 s. During the test, subjects sat comfortably in a chair in an office room under regular lighting conditions. One HC and four mild AD subjects who were unable to follow instructions were excluded from all statistical analyses.

2.4. Testing procedures and data analysis

Electroencephalographic (EEG) activity was recorded from 7 electrode sites (Fz, Cz, Pz, F3, P3, F4, and P4) of the international 10-20 system [21] using a COGNISION Headset (Neuronetrix). Electrodes were referenced to averaged mastoids (M1, M2), and Fpz served as the common electrode. The headset used for data collection has been validated to perform reliable ERP recordings when skin contact impedance is $<$70 kΩ, a practical requirement for recording in standard office environments. Impedance was automatically checked at all electrodes after each target or distractor tone, and was kept below this limit throughout each test. Data were collected from $-$240 to 1000 ms around the