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A Novel Eigenvector-based Method to Detect Mild Alzheimer's Disease Using Event-related Potentials

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Abstract

Event-related potentials (ERPs) are a physiological measure of cognitive function that have shown diagnostic and prognostic utility in Alzheimer's disease (AD). In this study, we used a novel eigenvector-based technique to better understand brain electrophysiological differences between subjects with mild AD and healthy controls (HC). Using ERPs from 75 subjects with mild AD and 95 HC, we first calculated cognitive task eigenvectors within each subject from three conditions and then calculated second-order eigenvector components to compare the AD group to the HC group. A MANOVA of the three second-level components discriminated between AD and HC multivariately (Wilks' lambda=.4297, $p<0.0001$, $R2 = .5703$), and also on each of the three components univariately (all 3 p-values<0.0001). The eigenvector-based technique used in this study accurately discriminated between the mild AD group and HC. As such, this analysis method adds to our understanding of the differences in ERP signal between AD and HC, and could provide a sensitive biomarker for diagnosis and monitoring of AD progression.

Key words: Event-related potentials, Alzheimer's disease.

Introduction

Alzheimer's disease (AD) is the most common type of dementia, affecting 44 million people worldwide with projections of up to 100 million people affected by 2050 (1). Neuropathologically characterized by amyloid beta plaques, neurofibrillary tangles composed of hyperphosphoralated tau, and neuronal loss, AD results in cognitive decline progressing to dementia (2).

Although the economic burden of AD in the United States is higher than that of cardiovascular disease or cancer (3), there are far more clinical trials testing new treatments for cancer than AD (4). This disparity is likely due in part to the challenge of successfully developing drugs effective in the latter. Cummings et al. (5) found a failure rate of 99.6 percent in clinical trials for AD, confirming that drug development in this area is an expensive and risky prospect.

The definitive diagnosis of AD requires neuropathological confirmation (6). Molecular biomarkers can help diagnosis and monitoring of the disease (7). However, the clinical application of these biomarkers has been challenging due to their complex relationship with clinical endpoints (5). Objective physiological measures of cognitive performance such as ERPs could provide information that is complementary to molecular biomarkers (8), and provide clinicians with a more complete clinical picture of dementia patients.

Many people affected by AD are diagnosed when the disease is past its early stages, thus delaying treatment (9). The use of a sensitive biomarker of AD could help with early detection, thus providing a useful window for intervention when the treatments might be more effective.

In this study, we used an eigenvector-based analysis on the ERP signal (10) to investigate whether this approach could discriminate AD subjects in the early stages of disease from HC.

Method

Subjects

We obtained ERP data recorded from 99 mild AD subject that met NINCDS-ADRDA criteria (11) for the disease, and 100 age-matched HC (Clinical Trials registration number: NCT00938665). Subjects' age ranged from 60 to 90 years. The study was conducted across seven sites in the United States. Appropriate institutional review boards approved the study, and all subjects provided informed consent.

In addition to a diagnosis of AD, inclusion criteria for the mild AD group required a Mini-Mental State Examination score between 21 and 26, a Clinical Dementia Rating score from 0.5 to 2.0, and delayed-recall scores on the Wechsler Logical Memory II subscale of less than 4 for 0-7 years of education, less than 6 for 8- 15 years of education, and less than 10 for 16 or more years of education. HC had a MMSE of 27 or higher, a Clinical Dementia Rating score of 0, and delayed-recall scores

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on the Wechsler Logical Memory subscale of 4 or higher for 0-7 years of education, 6 or higher for 8-15 years of education, and 10 or higher for 16 or more years of education.

Exclusion criteria for the study were use of antidepressant medication except SSRIs, or the presence of major psychiatric and neurological diseases (other than Alzheimer's for the AD group). Moreover, study enrollment required a modified Hachinski score of 4 or less, and a Geriatric Depression Scale Short Form score of 5 or less. Finally, all subjects were asked to withhold sedatives and dietary memory supplements for the 72 hours before testing.

Experimental Paradigm and Testing Procedures

Study subjects were tested using a three-stimulus oddball paradigm. Stimuli comprised of standard tones (1000Hz), target tones (2000Hz) and unexpected distractor tones (white noise) presented in pseudorandom order, so that target and distractor tones were never presented sequentially (Henry, Kaye, Bryan, Hutchison, & Ito, 2014). For each test, between 300 and 400 stimuli were presented binaurally through insert ear phones at 70dB volume. Subjects were instructed to respond to the target stimuli by pressing a button with their dominant hand.

Electroencephalographic (EEG) activity was recorded from 7 electrode sites (Fz, Cz, Pz, F3, P3, F4 and P4) of the international 10-20 system (Jasper, 1958) using a COGNISION™ Headset (Neuronetrix). Data was collected from –240 to 944ms around the stimuli, digitized at at 125 Hz, and bandpass filtered from .3 to 35 Hz. An artifact threshold of ±100 μV was set for the tests.

Analysis

Trials averaging to generate the ERP waves was automatically done by the COGNISION™ System software (Neuronetrix). EEG data from each trial were baseline corrected using the 240ms pre-stimulus period and averaged according to stimulus. For standard tones, only the trials immediately preceding target and distractor tones were averaged. Trials with a response that exceeded 2 times the RMS value were rejected and excluded from analysis.

ERP waves from all recording channels were used for the analysis. Based on spectral decomposition of correlation matrices from noninvasive ERPs obtained while the subjects participated in the auditory oddball cognitive task, we extracted three cognitive-task eigenvector components for each subject: one for the contrast between the target stimulus and the other two stimuli, one for anterior versus posterior electrode placement, and one for left versus right electrode placement. We next analyzed the primary eigenvectors to extract second-level between-person cognitive eigenvector components showing the differences between AD subjects and HC for each of the three conditions.

Results

The final sample consisted of 75 AD subjects and 95 HC due to missing data relevant to the analysis. The method discriminated among the three experimental cognitive-task conditions within single subjects with F ratios (signal to noise ratios squared) ranging from 21 to 162729. The three second-level cognitive components discriminated between AD and HC on the multivariate test of the MANOVA (Wilk's lambda = 0.4297, $p < 0.0001$, R2 = 0.5703), as did each of the univariate tests on the three between-persons components: target stimulus versus other stimuli: $F(1,168) = 81.02$, $p < 0.0001$, R2 = 0.3254, anterior versus posterior electrode positons: $F(1,168) = 53.24$, $p < 0.0001$, R2 = 0.2406, and left versus right electrode positions: $F(1,168) = 123.07$, $p < 0.0001$, R2 = 0.4228.

Visual inspection of the scatterplot (Figure 1) showed that the best separation between AD subjects and HC is in the two-dimensional plane defined by the vertical axis (target stimulus versus the other stimuli), and the horizontal axis corresponding to anterior versus posterior electrode placement. The separation is substantially weaker along the third axis, which extends from the left front face of the figure to the back right face, and corresponds to left versus right electrode placement.

Figure 1. Pattern of the location of each of the 75 AD subjects (black dots) and the 95 healthy controls ("h" symbols), with the left-to-right horizontal axis corresponding to the coefficients for the cognitive component left-to-right electrode location, the vertical axis corresponding to the coefficients for the cognitive component for target versus other stimuli separation, and the back-to-front horizontal axis corresponding to the coefficients for the cognitive component for posterior-to-anterior electrode location

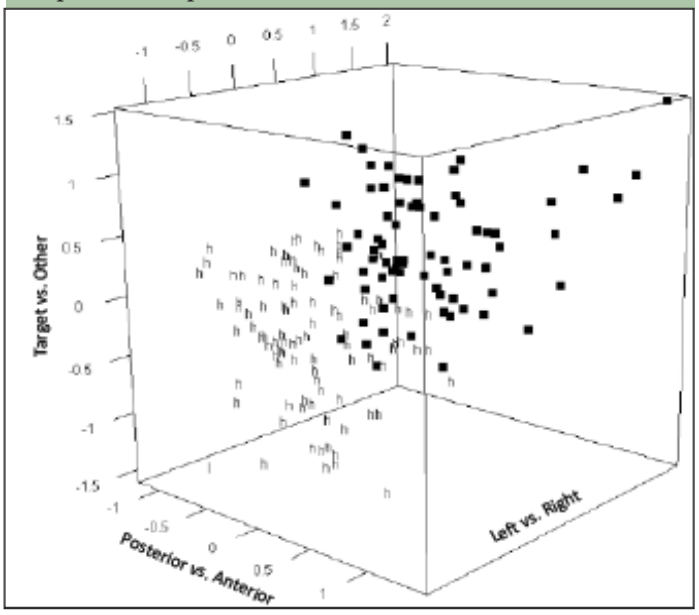
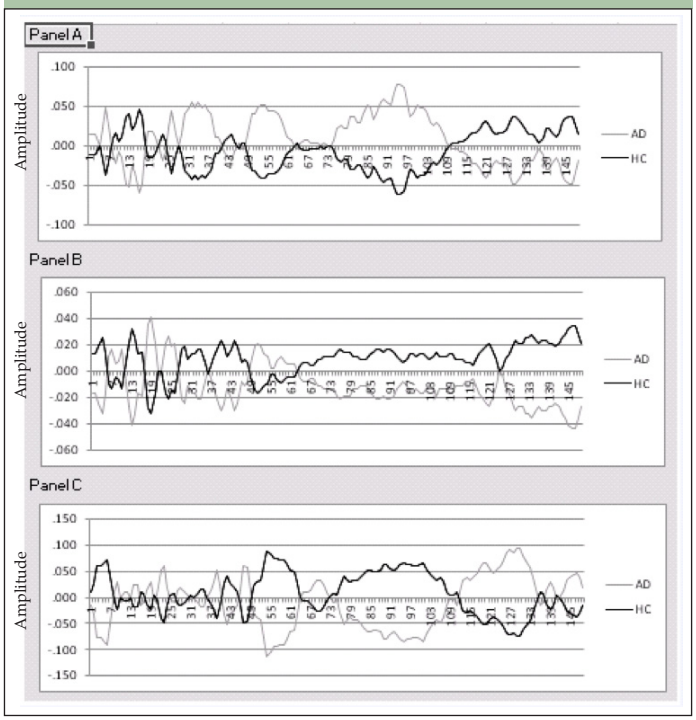


Figure 2. Envelope plots for each of the three second-order cognitive components which show the contrast between AD subjects and healthy controls across 1184 ms of the wave contours. Panel A shows these results for the discriminative component based on target stimulus versus other stimuli. Panel B shows these results for the discriminative component based on front versus back electrode locations. Panel C shows these results from the discriminative component based on left versus right electrode locations



Multiplying the vectors for the contours of the three components by the mean coefficients of the AD subjects and the HC, we constructed envelope plots for each of the three second-order cognitive components which were calculated to maximally discriminate between the two groups (Figure 2). The envelope plots show the points of major and minor contrast between the AD and HC group at each temporal location along the x-axis. The major contrast for the first component, based on target versus other, is between 336 and 640 ms, which is slightly to the right of the common location for the P300 ERP component. The major contrast for the second component, based on anterior versus posterior electrode locations, is to the right of 752 ms and is negative for AD. For the third component, based on left versus right electrode position, the major contrasts between the two groups are in two adjoining intervals, the first between 360 and 632 ms and the second between 632 ms and 832 ms.

Discussion

This novel eigenvector-based method of analyzing ERP data accurately discriminated between subjects with mild AD and age-matched HC.

The discrimination between groups based on the target stimulus suggests a difference in cognitive processing that is already present in the mild stages of the disease. The left-right electrode location discrimination could be due to asymmetrical pathological changes between right and left cortical or subcortical areas or to pathological changes in connections between the two hemispheres. This last hypothesis is consistent with findings showing abnormalities in the corpus collosum in AD (14). The discrimination between anterior and posterior electrodes suggests the possibility of cortical disconnection; this possibility is consistent with previous studies of EEG coherence that show evidence of a break down of cortical networks in subjects with AD (15).

The subjects in this study were selected to have mild AD. It will be important to determine whether our findings can be generalized, and whether the eigenvector-based method used in our analysis can discriminate between HC from subjects at all stages of the disease, from mild cognitive impairment (MCI) to severe AD. Further, it will be interesting to see if our analysis method can be used to discriminate asymptomatic subjects at risk of AD from those that are not. Similarly, it will be important to assess whether this method might have utility in monitoring or predicting response to treatment in AD.

In this study, we extracted only three cognitive eigenvector components for each subject: one for the contrast between the target stimulus and the other two stimuli, one for anterior versus posterior electrode placement, and one for left versus right electrode placement. Inclusion of additional eigenvector components, such as sex, genetic polymorphisms, baseline characteristics and data from other biomarkers could improve the discrimination between the AD and HC. Increasing the complexity of the ERP task may also improve discrimination.

In conclusion, this pilot study suggests that the use of eigenvectors obtained from ERP components which correspond to different conditions are able to accurately discriminate between subjects with early AD and HC. This indicates that eigenvector-based techniques may be able to serve as biomarkers for identifying subjects with the disease, and suggest that these analysis methods might be helpful for monitoring disease progression and investigating responses to treatment.

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Conflict of interest: B. Brown, S. Hendrix and D. Hedges have a patent pending related to the analysis methodology applied to the ERP curves. No conflicts are reported by the remaining authors.

Ethical standards: All procedures were in accordance with the Declaration of Helsinki (1975) as revised in 2013 and were approved by the responsible institutional review board. Informed consent was obtained from all subjects in the study.

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