Event-related potential markers of brain changes in preclinical familial Alzheimer disease

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ABSTRACT

Objectives: Event-related potentials (ERPs) can reflect differences in brain electrophysiology underlying cognitive functions in brain disorders such as dementia and mild cognitive impairment. To identify individuals at risk for Alzheimer disease (AD) we used high-density ERPs to examine brain physiology in young presymptomatic individuals (average age 34.2 years) who carry the E280A mutation in the presenilin-1 (*PSEN1*) gene and will go on to develop AD around the age of 45.

Methods: Twenty-one subjects from a Colombian population with familial AD participated: 10 presymptomatic subjects positive for the *PSEN1* mutation (carriers) and 11 siblings without the mutation (controls). Subjects performed a visual recognition memory test while 128-channel ERPs were recorded.

Results: Despite identical behavioral performance, *PSEN1* mutation carriers showed less positivity in frontal regions and more positivity in occipital regions, compared to controls. These differences were more pronounced during the 200–300 msec period. Discriminant analysis at this time interval showed promising sensitivity (72.7%) and specificity (81.8%) of the ERP measures to predict the presence of AD pathology.

Conclusions: Presymptomatic *PSEN1* mutation carriers show changes in brain physiology that can be detected by high-density ERPs. The relative differences observed showing greater frontal positivity in controls and greater occipital positivity in carriers indicates that control subjects may use frontally mediated processes to distinguish between studied and unstudied visual items, whereas carriers appear to rely more upon perceptual details of the items to distinguish between them. These findings also demonstrate the potential usefulness of ERP brain correlates as preclinical markers of AD. ***Neurology*® 2011;77:469–475**

GLOSSARY

AD = Alzheimer disease; **aMCI** = amnestic mild cognitive impairment; **ANOVA** = analysis of variance; **CERAD** = Consortium to Establish a Registry for Alzheimer's Disease; **EOG** = electro-oculography; **ERP** = event-related potential; **FAD** = familial AD; **LAI** = left anterior inferior; **LPS** = left posterior superior; **ROI** = region of interest.

Recognition memory impairments in Alzheimer disease (AD) have been linked to neocortical association areas including temporal and parietal lobes.[1] Event-related potentials (ERPs) are less expensive, more widely available, and more comfortable than many other imaging modalities (e.g., MRI, PET, SPECT). ERPs, along with other EEG measures, have proven to be a useful marker in neurodegenerative conditions.[2-5] ERP components of recognition memory are sensitive to decline in old age[6] and amnestic mild cognitive impairment (aMCI).[7] Studies have proposed ERPs as a sensitive method for early detection of AD, separating EEG activity related to AD pathology from normal aging.[8-12] Preclinical markers and early detection are increasingly

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Table 1 Subject demographic information and CERAD neuropsychological test battery[a]

	Controls (n = 11)	*PSEN1* carriers (n = 10)	*p* Value
Female, n	10	8	
Age, y	33.18 (6.06)	34.20 (6.40)	0.71
Range	24–40	25–43	
Education, y	11.90 (0.94)	11.80 (2.39)	0.89
Range	11–13	9–16	
MMSE/30	29.63 (0.67)	29.9 (0.31)	0.28
CERAD tests			
Verbal fluency	22.63 (4.78)	20.77 (3.86)	0.36
Naming/15	14.27 (0.78)	13.60 (0.66)	0.09
Memory words			
Total correct/30	20.27 (2.28)	21.60 (2.83)	0.25
Total intrusions	2.63 (2.80)	0.90 (0.87)	0.07
Recall of words			
Total correct/10	7.72 (1.19)	7.70 (0.94)	0.95
Total intrusions	0.54 (0.80)	0.10 (0.31)	0.12
Recognition of words			
Correct "yes"/10	9.63 (0.67)	9.90 (0.31)	0.27
Correct "no"/10	9.90 (0.30)	10 (0.00)	0.35
Constructional praxis/11	10.09 (0.83)	9.50 (0.84)	0.12
Recall of drawings/11	9.63 (1.96)	8.20 (1.18)	0.09

Abbreviations: CERAD = Consortium to Establish a Registry for Alzheimer's Disease; MMSE = Mini-Mental State Examination.
[a] Values denote mean ± SD.

important as research on new treatments that may slow or halt decline in AD are under development.[13,14]

Familial AD (FAD) allows the study of presymptomatic stages of AD that may be relevant for sporadic AD. Presenilin-1 (*PSEN1*) mutation carriers develop neuropathologic changes in cortical association areas and subcortical systems,[15] signs and symptoms that can be indistinguishable from those with sporadic AD, with a mean age of 45 at clinical onset.[16-19] Studies in FAD have demonstrated preclinical changes in morphometry,[20,21] regional brain activation,[22-24] functional connectivity,[25] and ERPs.[8,9] ERP preclinical changes have been shown in auditory stimulus discrimination[8] and semantic processing.[9] ERPs of recognition memory have not yet been evaluated in FAD.

Using an ERP picture paradigm proven sensitive to changes in recognition memory in older adults[6] and aMCI,[7] we examined young cognitively intact individuals who carry a *PSEN1* mutation causative of FAD.

METHODS

Participants. A total of 21 young participants were recruited from the Familial Colombian AD population studied at the University of Antioquia, Medellin, Colombia; 10 participants were carriers of the E280A *PSEN1* mutation and 11 were *PSEN1* mutation negative and served as controls. Participants had a minimum of 9 years of education. Groups were matched for age, sex, education, and neuropsychological assessment performance (table 1). Neuropsychological assessment consisted of the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) battery, which has been adapted to this Colombian population.[26] No participants had cognitive impairment as reported by their most recent neuropsychological assessment, which was done within 6 months prior to the time of the ERP session. Researchers were blind to the genetic status of the participants during data collection.

Standard protocol approvals, registrations, and patient consents. The study was approved by both the institutional review board committees of the University of Antioquia and Boston University. All subjects gave signed informed consent before participating.

Experimental materials and methods. Participants performed a recognition memory task using color pictures of concrete and namable objects: 50 new stimuli were presented during the study phase, and 100 stimuli (50% old) were presented during the test phase. The pictures used in the study were obtained from a stimuli set previously used by Ally et al.[7] and Ally and Budson.[27] Pictures were counterbalanced across study-test lists. In addition, test conditions (old, new) were counterbalanced across subjects. Color pictures were presented in central vision on a white background, with an average height of 13 cm and an average width of 15 cm, and a visual angle subtended of 7 degrees. All stimuli were presented on a 17-inch flat screen computer monitor positioned 48 inches from the subject. Each trial began with a 1,000-msec fixation character ("+") prior to the presentation of the stimuli. Study stimuli were then presented for 2,000 msec followed by the question, "Do you like this item?" Subjects were then prompted to button press to signify their like/dislike judgment and to remember the items for a subsequent memory test. Test stimuli were presented for 1,500 msec, followed by the question, "Is this item old or new?" Subjects were then prompted to button press to signify their old/new judgment. Subjects were asked to hold their responses until the question appeared immediately after stimuli presentation to minimize response-related ERP artifact. We acknowledge that asking participants to keep their response "in mind" (or alternatively, inhibiting their natural inclination to respond before the prompt) may affect the electrophysiologic data, particularly the late components. However, because subjects would be engaging in this activity in all trials, this activity should be removed when subtracting correct rejections from hits.

ERP procedure. Subjects were seated in a hardback chair and fitted with an Active Two-electrode cap (Behavioral Brain Sciences Center, Birmingham, UK). A full array of 128 Ag–AgCl BioSemi (Amsterdam, the Netherlands) "active" electrodes were connected to the cap in a preconfigured montage, which places each electrode in equidistant concentric circles from 10–20 position, Cz. In addition to the 128 scalp electrodes, minibiopotential electrodes were placed on each mastoid process. Finally, vertical and horizontal electro-oculography (EOG) ac-

tivity was recorded from bipolar electrodes placed below the left eye and on the outer canthus of the left and right eye. EEG and EOG activity were amplified with a bandwidth of 0.03–35Hz (3 dB points) and digitized at a sampling rate of 256 Hz. Recordings were referenced to a vertex reference point, but were later re-referenced to a common average reference to minimize the effects of reference site activity and accurately estimate the scalp topography of the measured electrical fields.[27] The sampling epoch for each test trial lasted for a total of 1,000 msec, which included a 200-msec prestimulus baseline period. This prestimulus period was used to baseline correct averaged ERP epochs lasting 800 msec. ERPs were averaged and corrected using the EMSE Software Suite (Source Signal Imaging, San Diego, CA). Trials were corrected for excessive EOG activity using the EMSE Ocular Artifact Correction Tool. The tool first allows the investigator to manually distinguish artifact data from artifact-free data. Then, using a covariance technique that simultaneously models artifact and artifact-free EEG, a logarithmic ratio of artifact data to clean data is produced by EMSE. Finally, ocular artifact is subtracted from the recording where it is detected by the correction tool. Trials were discarded from the analyses if they contained baseline drift or movement greater than 90 V. Individual bad channels were corrected with the EMSE spatial interpolation filter.

Behavioral analysis. Recognition accuracy was calculated using the discrimination index Pr (% hits − % false alarms) to compare the performance of the *PSEN1* mutation carriers and the controls. The discrimination values were submitted to a factorial analysis of variance (ANOVA) using group as between-subject factor.

ERP analysis. We performed 2 sets of analyses on the ERP data. For the first analysis, mean amplitudes were calculated for time intervals of every 100 msec from 0 msec to 800 msec (after stimulus presentation), which were then averaged across groups of 7 electrodes that formed 10 separate regions of interest (ROI) (central anterior inferior, left anterior inferior [LAI], right anterior inferior, left anterior superior, right anterior superior, left posterior superior [LPS], central posterior superior, right posterior superior, left posterior inferior, and right posterior inferior). An omnibus mixed-factor ANOVA was performed using the factors of group (*PSEN1* carriers and controls), item type (hits and correct rejections), time interval (0–100 msec, 100–200 msec, 200–300 msec, 300–400 msec, 400–500 msec, 500–600 msec, 600–700 msec, and 700–800 msec), and ROI (the 10 ROIs). Follow-up ANOVAs were performed as appropriate within time intervals and included the factors of group, item type, and ROI. Statistical analyses were performed using statistical software (SPSS version 16.0; SPSS Inc., Chicago, IL).

For the second analysis, we performed nonparametric permutation tests on the old/new scalp topographies for both groups. These permutation tests calculate the statistical probability of differences between groups or conditions in p values at every electrode for every millisecond without averaging across time.

The waveforms and scalp topographies were formed by averaging a series of trials for each subject; the mean number of trials for *PSEN1* carriers (36 hits and 36 correct rejections) and control subjects (38 hits and 36 correct rejections) was similar. All topographic maps represent an average of 100 msec going forward from the labeled time (e.g., "0 msec" represents the average from 0 to 99 msec).

Table 2 Significant effect and interactions from ANOVAs at every 100-ms interval from 0 to 800 ms

	F	Significance[a]
0–100 ms (ROI)	5.05	0.001
100–200 ms (item type[b] × ROI)	4.64	0.008
200–300 ms (item type[b] × ROI × group)	4.06	0.016
300–400 ms (item type[b] × ROI)	8.22	0.0005
400–500 ms (item type[b] × ROI)	15.37	0.0005
500–600 ms (item type[b] × ROI)	9.38	0.0005
600–700 ms (item type[b] × ROI)	5.98	0.003
700–800 ms (item type[b] × ROI)	4.72	0.010

Abbreviations: ANOVA = analysis of variance; ROI = region of interest.
[a] Only significant interactions are shown.
[b] Item type: hits and correct rejections.

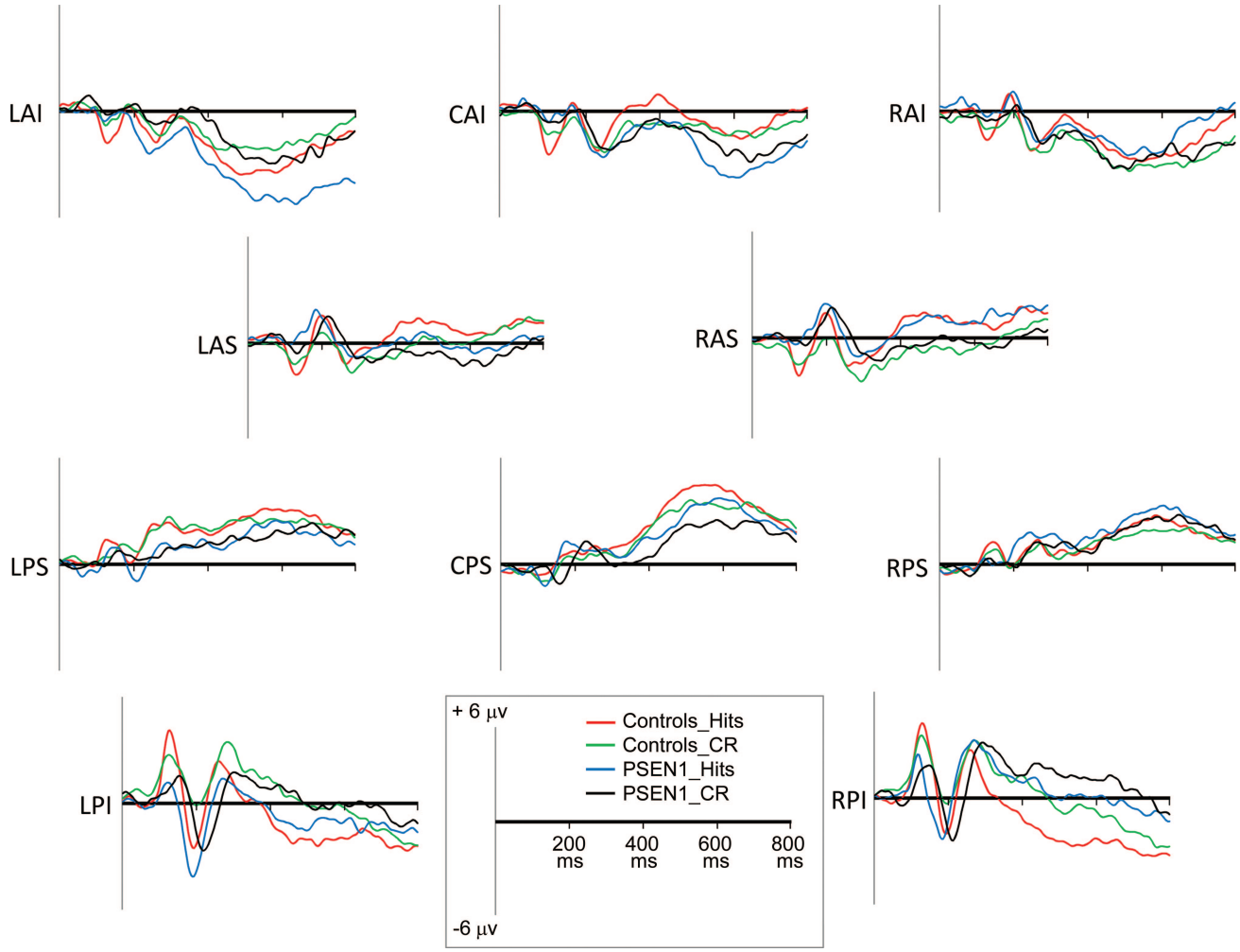
Stepwise discriminant analysis. Stepwise discriminant analysis was used on the time intervals in which there was a statistically significant interaction between group, item type, and ROI to quantify the ability of ERP measures to successfully classify individuals according to the FAD-related mutation.

RESULTS

Behavioral performance. Both groups performed near ceiling in terms of recognition memory discrimination (controls: 0.92, SD 0.03; *PSEN1* carriers: 0.92, SD 0.03). There was no significant difference in median reaction time between the controls (655.29 msec, SD 136.8) and *PSEN1* carriers (629.40 msec, SD 127.3) ($F_{1,19} = 0.39$, $p = 0.53$).

ERP results. ***ANOVAs.*** The initial omnibus mixed-factor ANOVA revealed significant interactions of item type, ROI, time interval, and group ($F_{1,63} = 1.71$, $p = 0.001$), ROI and time interval ($F_{1,63} = 7.23$, $p = 0.001$), item type and ROI ($F_{1,9} = 9.30$, $p = 0.001$), item type, ROI, and time interval ($F_{1,63} = 4.42$, $p = 0.001$). In order to understand the 4-way and other interactions, separate ANOVAs for each time interval were performed. Only the omnibus mixed-factor ANOVAs for the 200 to 300 msec interval revealed a significant interaction of item type, ROI, and group ($F_{1,9} = 4.06$, $p = 0.01$). Post hoc independent sample t tests for hits and correct rejections between groups at the 200–300 msec time interval revealed that hits at ROI left posterior superior (t [19] = 2.04, $p = 0.05$) were significantly less positive for *PSEN1* mutation carriers compared to controls. Correct rejections were significantly different between groups at ROI right anterior superior (t [19] = −2.40, $p = 0.02$), ROI left posterior superior (t [19] = 2.47, $p = 0.02$), and ROI left posterior inferior (t [19] = 2.10, $p = 0.04$). In this case, correct rejections were more positive for *PSEN1* carriers at ROI right anterior superior and more positive for

Figure 1 *PSEN1* carriers and controls grand average hit and correct rejection event-related potential (ERP) waveforms



Each waveform represents the composite average of the 7 electrodes subsuming 10 different regions of interest (ROI). ROIs are listed to the left of each waveform: central anterior inferior (CAI), left anterior inferior (LAI), right anterior inferior (RAI), left anterior superior (LAS), right anterior superior (RAS), left posterior superior (LPS), central posterior superior (CPS), right posterior superior (RPS), left posterior inferior (LPI), and right posterior inferior (RPI).

controls at ROI left posterior superior and ROI left posterior inferior. Paired sample t tests for hits vs correct rejections in *PSEN1* carriers alone showed that hits were more positive than correct rejections at ROIs right posterior superior (t [9] = 2.67, p = 0.02) and ROI right posterior inferior (t [9] = 2.74, p = 0.02), and more negative at ROI left anterior inferior (t [9] = −2.79, p = 0.02). A similar analysis in controls did not show any statistically significant differences.

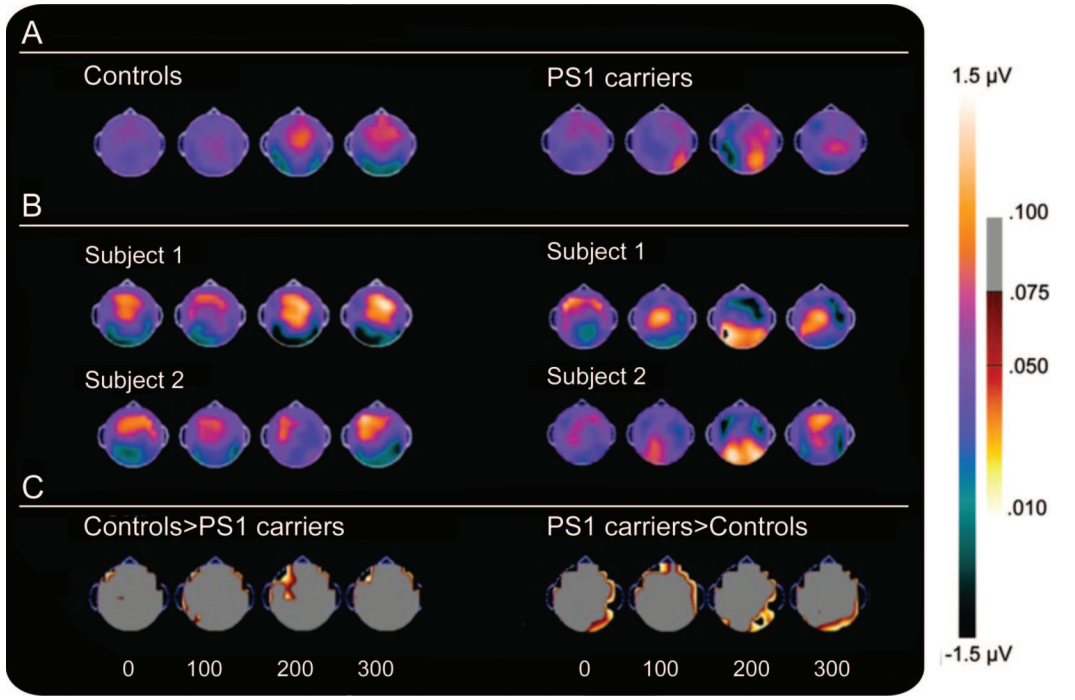
ANOVAs at other time intervals (100–200 msec, 300–400 msec, 400–500 msec, 500–600 msec, 600–700 msec, 700–800 msec) revealed significant interactions between item type and ROI, but not group (table 2).

Grand average hit and correct rejection ERP waveforms for *PSEN1* mutation carriers and controls can be seen in figure 1.

Nonparametric analyses. Scalp topography maps showed the expected old/new effect at right superior and inferior right frontal regions between 300 and 500 msec in both groups (figure 2A). Between-group nonparametric analyses revealed that the old/new effect was greater at bilateral frontal electrodes, with lesser extent in the left frontal regions for the *PSEN1* carriers compared to the controls. These frontal differences began early in the recording interval (~200 msec) and continued uninterrupted throughout most of the recording. The nonparametric analyses also revealed that the left frontal regions were less positive for the *PSEN1* carriers than for the controls, whereas a small area in the center posterior region was more positive for the *PSEN1* carriers than for controls from 650 to 800 msec. Right posterior regions were more positive for the *PSEN1* carriers compared to controls throughout most of the recording epoch, especially evident at early time intervals.

Topographic scalp distributions for representative individuals are shown in figure 2B. The early poste-

Figure 2 *PSEN1* carriers and controls old/new scalp topography maps



Topographies are presented in 100 msec averages going forward. (A) Averaged old/new scalp topographies for each group of subjects (controls and *PSEN1* carriers). (B) Old/new scalp topographies for 2 typical subjects from each group. (C) Results of the between-group nonparametric analysis showing the early event-related potential differences in the posterior regions.

rior differences evidenced by the nonparametric analyses during the time window 200–300 msec were observed at the individual level in 7 out 10 of the *PSEN1* carriers, but only in 3 out of 11 controls.

Stepwise discriminant analysis. To directly examine the predictive potential of the ERP measures, a stepwise discriminant analysis was also performed at the 200–300 msec interval with the 10 ROIs for hits and correct rejections. Prediction of a given subject's classification was based upon a model that did not include that subject. The output model included correct rejections at ROI LPS and hits at ROI LAI. A total of 81.8% (9/11) of control subjects and 72.7% (8/10) of *PSEN1* carriers were correctly classified ($\chi^2 = 11.194$, $df = 2$, $p = 0.004$).

DISCUSSION The present study found evidence to suggest that subtle differences in the neural processes associated with visual recognition memory occur very early in carriers of the *PSEN1* mutation, years before the onset of cognitive symptoms and the development of AD. While both groups evoked the characteristic ERP pattern during recognition memory, control subjects exhibited activation patterns reliably associated with frontally mediated processes that distinguish between studied and unstudied visual items,[27] while carriers exhibited more brain activity in occipital regions that have been associated with visual perceptual processing.[28] Increases of occipital activity have been reported previously in an ERP study of word recognition memory in patients with aMCI,[7] and in a PET study of successful verbal recognition in patients with mild AD.[29] AD is thought to cause a functional decline associated with posterior cortical dysfunction,[30] and a variety of visual disorders including impairments of contrast sensitivity, motion perception, and navigation have been associated with memory problems observed in AD.[28] The pattern of posterior activity observed in our *PSEN1* carriers may reflect an early AD-related synaptic dysfunction or a neural compensation process that requires that carriers recruit more the posterior regions during recognition memory in order to perform equally well as controls. These 2 processes may be impacting the way that their brains recognize items previously learned, and which may occur decades prior to recognizable cognitive symptoms. This would suggest that young presymptomatic *PSEN1* carriers rely more on bottom-up perceptual factors or physical features of the items to make recognition memory decisions, which in turn may help to maintain their level of performance on these tasks.

We identified in our study a pattern of ERP activity with promising sensitivity and specificity that may be able to identify individuals who are likely to

develop AD later in life. This potential finding is especially relevant with the advent of treatments that may ameliorate the effects of AD if applied early in its course or even prevent the disease. The pattern of ERP activity that best aided in the discrimination of the *PSEN1* carriers involved left posterior regions and left frontal regions. Structures in these regions have long been implicated in AD[31,32] and atrophy in these structures has been found to be predictive of disease progression.[33-35] The sensitivity and specificity of our results are comparable to studies using other ERP measures[8,36] as potential markers of preclinical AD. Thus, our analysis reveals a possible cognitive marker that may potentially aid early diagnosis, which needs to be confirmed with much larger population-based studies. In addition, future research is needed to determine whether ERP brain correlates as preclinical markers of AD may translate from familial to sporadic forms of the disease.

AUTHOR CONTRIBUTIONS

Y.T.Q., B.A.A., C.E.S., and A.E.B. designed experiments. Y.T.Q., A.L.R., and J.M. performed experiments. Y.T.Q., B.A.A., K.C., F.L., C.E.S., and A.E.B. analyzed and interpreted data. F.L. supervised work in Colombia. A.E.B. and C.E.S. supervised work in Boston. Y.T.Q., B.A.A., and A.E.B. wrote the manuscript.

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DISCLOSURE

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Morton Nathanson

Neurology **1988;38:504–505**

Descriptions of the phenomenon of phantom limbs by S. Weir Mitchell appeared in two lay periodicals before being published for the medical profession. S. Weir Mitchell (1829–1914), neurologist extraordinaire, one of the fathers of American neurology and respected popular literary figure of his time, is credited with the first careful clinical investigation and explanation of what he referred to as the "phantom limb." Mitchell acknowledged that "the feelings and delusions of men who had lost members have often been the subjects of casual notice in surgical treatises from as far back as Ambrose Park's time."

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Comment from Robert A. Gross, MD, PhD, FAAN, Editor-in-Chief: *One of our earliest Historical Neurology contributions, this study detailed the contributions—in the lay press!—of one of this country's early neurologists, practicing during the Civil War.*