Event-Related Potential Changes in Groups at Increased Risk for Alzheimer Disease

Joanne Green, PhD; Allan I. Levey, MD, PhD

Background: Individuals who have a family history (FH) of Alzheimer disease (AD) or who carry the apolipoprotein E ε4 allele are at increased risk for developing AD. Abnormalities in brain event-related potentials (ERPs) have been observed in patients diagnosed as having AD.

Objective: To determine whether groups of nonsymptomatic, middle-aged individuals at increased risk for AD exhibited ERP changes consistent with this disease.

Design: In a case-control study, ERPs were elicited using an auditory oddball paradigm, and a brief neuropsychological battery was administered.

Setting: University laboratory facilities.

Subjects: We compared age-matched and education-matched groups with a positive family history (FH+; n = 24) or a negative family history (FH−; n = 23) of AD. Within the FH+ group, subgroups were identified as either carriers of the apolipoprotein E ε4 allele (ε4+; n = 9) or noncarriers (ε4−; n = 8), and these subgroups were compared with the FH− group.

Main Outcome Measures: The latency and amplitudes of P3, N2, and P2 components of the ERP were quantified and analyzed statistically.

Results: Compared with the FH− group, both the whole FH+ group and the FH+/ε4+ subgroup showed abnormal prolongation in the latency of the P3 component. In addition, the FH+/ε4+ subgroup showed abnormal prolongation in the latency of the N2 component. These changes were observed in the absence of neuropsychological deficits.

Conclusions: The findings indicate that groups at increased risk for developing AD show ERP changes consistent with those observed in patients diagnosed as having AD. The results support accumulating evidence that AD has a preclinical phase and that early detection may be possible.

Arch Neurol. 1999;56:1398-1403

RESULTS

NEUROPSYCHOLOGICAL AND BEHAVIORAL DATA

Neuropsychological and behavioral data are shown in the Table. There were no significant differences between groups, ei-
SUBJECTS AND METHODS

SUBJECTS

Twenty-four FH+ individuals were compared with 23 individuals with a negative family history (FH−). Subjects were excluded if they had a history of neurologic, psychiatric, or other disease that might predispose them to cognitive dysfunction or cerebral ischemia. Each of the subjects reported normal hearing. Individuals in the FH+ group met 2 criteria: (1) they had at least 1 parent with a progressive dementia diagnosed as late-onset AD by a physician; and (2) they had another relative in that lineage who had either physician-diagnosed AD or a dementia of unidentified origin consistent with AD based on available information. The mean (SD) age of disease onset for the parents of the FH+ group was 72.9 (5.0) years, based on subject report. The FH+ and FH− groups did not differ significantly in years of age (mean [SD]: FH+: 55.5 [5.0]; FH−: 55.4 [4.4]) or years of education (mean [SD]: FH+: 14.4 [2.0]; FH−: 15.1 [2.3]). Subjects were recruited through newsletter advertisements and signed informed consent forms that were approved by the Emory University Human Investigations Committee, Atlanta, Ga.

DNA EXTRACTION AND APOE GENOTYPING

The APOE genotyping was performed in 17 of 24 of the FH+ subjects using procedures described previously. The 7 remaining FH+ subjects were unable to return for blood sampling. Among the 17 FH+ subjects, the genotypes were as follows: 4 were e4/4, 5 were 3/4, 6 were 3/3, and 2 were 2/3. Thus, 9 (53%) of the sampled subjects carried at least 1 APOE e4 allele, and 8 (47%) of the FH+ subjects did not carry an APOE e4 allele (E4−). The percentage of the FH+ subjects carrying the APOE e4 allele is higher than previously reported (32% and 36%), but this may reflect either the small sample size or the requirement that the FH+ subjects have 2 blood relatives (not just 1) in the same lineage with probable AD. The 2 FH+ subgroups did not differ significantly in years of age (mean [SD]: FH+/e4+, 58 [5.1]; FH+/e4−, 54 [4.7]) or years of education (mean [SD]: FH+/e4+, 14.7 [2.2]; FH+/e4−, 15 [2.3]), nor did they differ significantly from the FH− group.

PROCEDURES

The P3 component was assessed with an auditory oddball paradigm using data collection and analysis procedures previously described. The primary interest was in the P3 recorded at Pz, an electrode location at which abnormalities in patients with AD have been observed. Data also were recorded at locations Fz and Cz. The P3 component was identified as the largest positive peak between 250 and 300 milliseconds following the oddball tone and having maximal parietocentral amplitude. The P3 peak amplitude was computed by subtracting the 150-millisecond prestimulus baseline, and the peak latency was computed relative to stimulus onset. The P2 and N2 components were identified and quantified using conventional procedures.

Subjects underwent a brief neuropsychological battery including behavioral measures, particularly of delayed memory, that are sensitive to symptoms of early AD. The battery included the California Verbal Learning Test (Trial 1-5 cumulative learning, Trial 3 recall, long-delay free recall, and long-delay discriminability), Wechsler Adult Intelligence Scale-Revised Block Design (total points), and Digit Symbol (total points), and the Beck Depression Inventory. One FH− subject was unable to complete the battery due to time constraints, and 1 FH+ subject did not complete the Beck Depression Inventory.

DATA ANALYSIS

Two sets of comparisons were made for each variable. The first set compared groups as a function of FH alone (FH+ compared with FH−). The second set compared groups in terms of relative risk: (1) the FH+/e4+ subgroup with an increased risk due to FH and APOE e4 genotype; (2) the FH+/e4− subgroup with an increased risk due to FH but not APOE e4 genotype; and (3) the FH− group with a low risk due to FH.

For each ERP component, latency and amplitude were analyzed separately. Data meeting assumptions of homogeneity of variance were analyzed using a mixed design analysis of variance with group (either FH or APOE e4 genotype) as a between-groups factor and electrode (Fz, Cz, and Pz) as a repeated measure. Significant interactions were analyzed by planned comparison of means. If assumptions of homogeneity of variance were violated, groups were compared at each electrode location using nonparametric statistics (Kruskal-Wallis or Mann-Whitney test). A similar approach was used in making group comparisons of each of the neuropsychological measures and of the median reaction time obtained from the auditory oddball paradigm.

Figure 1, there also tended to be a group difference as a function of electrode location (F2,90 = 2.8; P = .06). The mean (SE) P3 latency at Pz was significantly longer for the FH+ group (397 [8.2] milliseconds) than it was for the FH− group (375 [6.2] milliseconds) (t15 = 2.0; P = .047), although the latency of the 2 groups did not differ at the other electrode locations (P = .84 and P = .71 for Cz and Pz, respectively). The small but significant difference in P3 latency at Pz is further illustrated in the ERP wave forms for the FH+ and FH− groups shown in Figure 2. Thus, consistent with the initial hypothesis, the FH+ group showed abnormal prolongation of P3 latency measured at Pz.

in Figure 1, there also tended to be a group difference as a function of electrode location (F2,90 = 2.8; P = .06). The mean (SE) P3 latency at Pz was significantly longer for the FH+ group (397 [8.2] milliseconds) than it was for the FH− group (375 [6.2] milliseconds) (t15 = 2.0; P = .047), although the latency of the 2 groups did not differ at the other electrode locations (P = .84 and P = .71 for Cz and Pz, respectively). The small but significant difference in P3 latency at Pz is further illustrated in the ERP wave forms for the FH+ and FH− groups shown in Figure 2. Thus, consistent with the initial hypothesis, the FH+ group showed abnormal prolongation of P3 latency measured at Pz.
The mean (SE) P3 amplitude was 12.9 (0.8) µV and did not vary significantly as a function of FH (P = .75) or electrode location (P = .10).

Comparison of Risk Groups

Figure 3 shows the P3 latency data for the 3 risk groups. There were significant group differences at electrodes Pz (H² = 6.8; P = .03) and Cz (H² = 6.2; P = .04). At each of these electrodes, the P3 latency of the FH+/e4+ subgroup was significantly longer than that for the FH− group (P = .009 and P = .02 for Cz and Pz, respectively). Other between-group comparisons did not reveal significant differences. The P3 latency difference between the FH− and FH+/e4+ groups is further illustrated in the ERP wave forms shown in Figure 4. Thus, the abnormal prolongation of P3 latency was pronounced for the FH+/e4+ subgroup.

The P3 amplitude did not vary significantly as a function of FH or electrode location (P = .75) or electrode location (P = .10).

Comparison of FH Groups

Figure 2 shows the P3 latency data for the 3 risk groups. There were significant group differences at electrodes Pz (H² = 6.8; P = .03) and Cz (H² = 6.2; P = .04). At each of these electrodes, the P3 latency of the FH+/e4+ subgroup was significantly longer than that for the FH− group (P = .009 and P = .02 for Cz and Pz, respectively). Other between-group comparisons did not reveal significant differences. The P3 latency difference between the FH− and FH+/e4+ groups is further illustrated in the ERP wave forms shown in Figure 4. Thus, the abnormal prolongation of P3 latency was pronounced for the FH+/e4+ subgroup.

The P3 amplitude did not vary significantly as a function of FH or electrode location (F²,74 = 3.3; P = .04). The mean (SE) P3 amplitude was larger at Pz (13.7 [0.9] µV) than it was at Fz (12.5 [0.8] µV) (P = .02). However, the mean (SE) Cz amplitude (12.4 [1.0] µV) did not differ from that at the other 2 locations.

N2 COMPONENT

Comparison of FH Groups

Neither N2 latency nor amplitude showed significant variation as a function of FH or electrode location. In Figure 2, although the mean (SE) amplitude of the N2 component appears to be smaller for the FH+ group (3.4 [6.5] µV) than it is for the FH− group (5.8 [8.6] µV), this difference did not approach statistical significance (P = .57).

Comparison of Risk Groups

The N2 latency varied significantly across electrodes, the FH+/e4+ group (254 [5.7] milliseconds) was significantly longer than that of the FH+/e4− group (231 [3.7] milliseconds; P = .02) or the FH− group (235 [2.6] milliseconds; P = .04). This pattern was consistent among all 3 electrode locations.

The mean (SE) P3 amplitude was 12.9 (0.8) µV and did not vary significantly as a function of FH (P = .75) or electrode location (P = .10).

Comparison of Risk Groups

Figure 3 shows the P3 latency data for the 3 risk groups. There were significant group differences at electrodes Pz (H² = 6.8; P = .03) and Cz (H² = 6.2; P = .04). At each of these electrodes, the P3 latency of the FH+/e4+ subgroup was significantly longer than that for the FH− group (P = .009 and P = .02 for Cz and Pz, respectively). Other between-group comparisons did not reveal significant differences. The P3 latency difference between the FH− and FH+/e4+ groups is further illustrated in the ERP wave forms shown in Figure 4. Thus, the abnormal prolongation of P3 latency was pronounced for the FH+/e4+ subgroup.

The P3 amplitude did not vary significantly as a function of FH or electrode location (P = .75) or electrode location (P = .10).

Comparison of FH Groups

Figure 2 shows the P3 latency data for the 3 risk groups. There were significant group differences at electrodes Pz (H² = 6.8; P = .03) and Cz (H² = 6.2; P = .04). At each of these electrodes, the P3 latency of the FH+/e4+ subgroup was significantly longer than that for the FH− group (P = .009 and P = .02 for Cz and Pz, respectively). Other between-group comparisons did not reveal significant differences. The P3 latency difference between the FH− and FH+/e4+ groups is further illustrated in the ERP wave forms shown in Figure 4. Thus, the abnormal prolongation of P3 latency was pronounced for the FH+/e4+ subgroup.

The P3 amplitude did not vary significantly as a function of FH or electrode location (F²,74 = 3.3; P = .04). The mean (SE) P3 amplitude was larger at Pz (13.7 [0.9] µV) than it was at Fz (12.5 [0.8] µV) (P = .02). However, the mean (SE) Cz amplitude (12.4 [1.0] µV) did not differ from that at the other 2 locations.

N2 COMPONENT

Comparison of FH Groups

Neither N2 latency nor amplitude showed significant variation as a function of FH or electrode location. In Figure 2, although the mean (SE) amplitude of the N2 component appears to be smaller for the FH+ group (3.4 [6.5] µV) than it is for the FH− group (5.8 [8.6] µV), this difference did not approach statistical significance (P = .57).

Comparison of Risk Groups

The N2 latency varied significantly across electrodes, the FH+/e4+ group (254 [5.7] milliseconds) was significantly longer than that of the FH+/e4− group (231 [3.7] milliseconds; P = .02) or the FH− group (235 [2.6] milliseconds; P = .04). This pattern was consistent among all 3 electrode locations.
plasma levels of CRP and IL-6 were significantly higher in the 

Comparison of Risk Groups

Neither P2 latency nor P2 amplitude showed significant variation as a function of risk group or electrode.

RELIABILITY ANALYSIS

The reliability of ERP measures showing significant variation as a function of FH or risk group was examined. For each subject, the first and second halves of the ERP trials were signal averaged separately, and the latency was identified for each half. The Pearson r correlation was computed between the latencies of the first and second half of the trials and then adjusted with the Spearman-Brown formula to determine the split-half reliability. The number of data pairs available for these analyses varied because inclusion of only half of the data in the signal averaging resulted in a noisy ERP wave form that made it impossible to identify some components and peak latencies for a few subjects.

For the data in the FH group comparison, there was a significant correlation between the first and second half P3 latency at Pz (r_{36} = 0.55; P < .001). For data in the risk group analysis, there were significant correlations between first and second half P3 latency at either Cz or Pz (r_{39} = 0.87 and r_{39} = 0.62, respectively; each at P < .001) and for N2 latency at Fz, Cz, or Pz (r_{17} = 0.84, r_{17} = 0.88, and r_{17} = 0.73, respectively; each at P < .001). These findings support the reliability of these measures.

P2 COMPONENT

Comparison of FH Groups

Neither P2 latency nor amplitude varied significantly as a function of FH (P = .18 and P = .96, respectively). The P2 latency did show small but significant variation as a function of electrode location (F_{2,30} = 4.0; P = .02). The mean (SE) P2 latency was shorter at Cz (178 [2.4] milliseconds) than it was at Pz (184 [4.2] milliseconds; P = .02) or Fz (185 [2.4] milliseconds; P = .01). The P2 amplitude also showed significant variation as a function of electrode location (F_{2,30} = 5.1; P = .01). The mean (SE) P2 amplitude was greater at Fz (4.0 [0.5] μV) than it was at Pz (2.5 [0.5] μV; P < .001), but the mean (SE) amplitude did not vary significantly between these electrodes and Cz (3.3 [0.6] μV; P = .13 for Fz compared with Cz; P = .10 for Pz compared with Cz).

The purpose of this study was to evaluate the hypothesis that ERP components would show abnormal change in groups of nonsymptomatic, middle-aged individuals with arterial hypertension.
at increased risk for AD. The results supported the hypothesis. The FH+ group had abnormally prolonged P3 latency compared with the FH− group. Furthermore, the FH+/e4+ subgroup had significant P3 latency prolongation compared with the FH− group, while the FH+/e4− subgroup did not show this prolongation.

In addition, the FH+/e4− subgroup also showed abnormality in N2 latency. The N2 component reflects processing activities involved in stimulus classification preceding more memory-dependent processes reflected in the P3 component. In patients with AD, N2 latency prolongation sometimes accompanies P3 latency abnormality, and the N2 may be the first ERP component to show latency abnormality in very mild AD. Therefore, the finding of N2 latency abnormality in the FH+/e4+ subgroup supports the existence of ERP abnormalities in preclinical AD.

The significant P3 and N2 changes are particularly impressive since they occurred in individuals, some of whom will never develop AD and are considerably younger than their affected relatives. Although the latency prolongation in the FH+/e4+ subgroup was small, the mean subject age of 58 years is 15 years younger than the age at which their affected relatives became clinically symptomatic. Thus, even those individuals who will eventually develop AD are in a preclinical phase during which electrophysiological dysfunction may be subtle. In addition, the true P3 latency abnormality associated with preclinical AD is probably diluted in the present study because not all of the FH+/e4+ individuals will develop AD, and some of the FH+/e4− individuals will develop AD.

In this study, the FH+/e4− subgroup did not show P3 or N2 abnormalities compared with the FH− group. Since APOE ε4 allele dose has been related to both disease risk and age of disease onset, the FH+/e4− subgroup may have normal P3 components because most members will never develop AD or are currently at an earlier preclinical stage compared with the FH+/e4+ group. The absence of ERP abnormalities in the FH+/e4− subgroup is consistent with the absence of metabolic abnormalities observed by others.

These results augment those of a previous study that associated ERP abnormalities with an FH+ of AD. Boutros and colleagues observed that nonsymptomatic individuals who had first-degree relatives with autopsy-proven AD exhibited abnormally increased P3 amplitude, although the P3 latency was not abnormal. Elevation of P3 amplitude may reflect abnormal exertion of mental effort in patients with brain disease. However, even when we recalculated P3 amplitude using their peak-to-peak approach, we did not observe P3 amplitude abnormality in either the FH+ group or the FH+/e4− subgroup. Important methodological differences may explain the variations in findings, including subject selection and technical aspects of eliciting and measuring the P3 amplitude. Nevertheless, both our study and that of Boutros and colleagues are consistent in observing P3 abnormalities in groups at increased risk for AD.

In summary, the results support accumulating evidence that AD has a preclinical phase. These findings augment previous research in suggesting that groups at increased risk for AD show changes in the P3 and N2 components of the ERP, in addition to the metabolic and neuropsychological changes previously described by others. The findings raise the possibility that assessment of ERPs may contribute to early detection of AD, and future research should examine approaches for increasing the sensitivity of these measures for detecting abnormality in individual patients.

Accepted for publication September 22, 1998.

This work was supported by the Emory University Alzheimer’s Disease Center, Atlanta, Ga, and grant AG-10130 from the National Institute on Aging, Bethesda, Md.

We are grateful to Suzanne S. Mirra, MD, Marla Gear- ing, PhD, and Douglas C. Wallace, PhD, for performing the genotyping, and to Brett E. Sirockman, Stella C. Harper, and Amy Cosby for assistance in data collection.

Reprints: Joanne Green, PhD, Department of Neurology, Emory University School of Medicine, Wesley Woods Center, 1841 Clifton Rd, Atlanta, GA 30329 (e-mail: jgreen@emory.edu).

REFERENCES


