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ApoE genotype and abnormal auditory cortical potentials in healthy older females☆

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Abstract

Apolipoprotein E (ApoE) status and gender are risk factors for the development of Alzheimer's disease. Alzheimer's disease is more prevalent in female relative to male carriers of the ApoE ε4 gene. We examined cortical sensory (P50, N100) and cognitive (P300) potentials in an auditory target detection task in females as a function of ApoE genotype (ApoE ε4 carriers, ApoE ε4 non-carriers) to define the incidence of abnormalities prior to the clinical expression of cognitive impairments. Both neuropsychological test scores and sensory cortical potentials did not differ between the two ApoE groups. In contrast, cognitive P300 potentials were significantly decreased in amplitude and delayed in latency for ApoE ε4 carriers compared to non-carriers. Four out of the 10 ApoE ε4 carriers had abnormally (>2S.D.) delayed P300 latency compared to one out of 20 non-carriers. Abnormal cognitive processes reflected by P300 latency delays are expressed at significantly higher incidence in normal older females who are carriers of the ε4 allele than in non-carriers of this allele.

Keywords: Apolipoprotein E; Auditory event-related potentials; Aging; P300; P50

1. Introduction

Alzheimer's disease (AD) is a progressive neurodegenerative disorder that is characterized by the deposition of β-amyloid plaques and neurofibrillary tangles in selected regions of the brain (Braak et al., 1998; Price and Morris, 1999). Major risk factors for the development of AD include age, gender, and apolipoprotein E gene (ApoE) status (Morris, 2003). The ApoE gene has three alleles: ε2, ε3, and ε4. The ε2 allele has the lowest risk of AD, followed by ε3, with the greatest AD risk with ε4 (∼3 times higher than normal risk) (Poirier et al., 1993). Possession of the ε4 allele is also associated with memory decline in healthy normal aging (Packard et al., 2007). Moreover, the extent of the memory disorder is greater in ApoE ε4 carriers with amnestic mild cognitive impairment or AD compared to non-carriers with these disorders (Fleisher et al., 2005; van der Vlies et al., 2007). There is a dosage effect with greater risk and earlier onset of AD for ApoE ε4 homozygotes compared to heterozygotes (Corder et al., 1993). Higher prevalence rate of AD is also reported for female compared to male ApoE ε4 carriers (Farrer et al., 1997). Female ApoE ε4 carriers show greater decline in cognitive performance from the ages of 50–80 years compared to non-carriers whereas older males do not show this relationship (Mortensen and Høgh, 2001). Taken together, the greater risk of AD and age-related cognitive decline associated with ApoE ε4 in females suggest that healthy elderly females having ApoE ε4 may manifest asymptomatic changes of neural functions that can be detected by non-invasive neurophysiological measures.

Auditory target detection, or "odd-ball" tasks have been used to quantify activity of cortical sensory and cognitive functions. In the target detection task subjects press a button to infrequent (high-pitch) target tones that are embedded

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Table 1
Demographic information.

	ApoE ε4 carriers	ApoE ε4 non-carriers
n	10	20
Family history of AD[a]	2	4
Age (years)	69.8 ± 6.5	69.4 ± 5.8
Education (years)	15.5 ± 2.4	14.6 ± 2.0

[a] AD: Alzheimer's disease. Values are means ± standard deviations.

within a sequence of standard (low-pitch) tones (Sutton et al., 1965). Auditory cortical changes during normal aging are accompanied by increased amplitude of sensory P50 component to non-targets (Golob et al., 2007) and delayed latency of cognitive P300 component to targets (Goodin et al., 1978). Moreover, these P50 amplitude and P300 latency changes are enhanced in amnestic mild cognitive impairment (Golob et al., 2002, 2007). These changes of electrophysiological sensory and cognitive responses in amnestic cognitive impairment occur without accompanying behavioral dysfunctions (reaction times, accuracy) in keeping with the clinical experience that symptomatic expression of a disorder may be delayed relative to the finding of laboratory measures of abnormality.

In this report, we characterized a group of "normal" older females by the ApoE genotype, neuropsychological tests, and brain potentials during an auditory target detection task. We hypothesized that in "normal cognitive functioning" ApoE ε4 carriers both sensory P50 component to non-targets and cognitive P300 component to targets would show changes that exceed those found in non-carriers. Moreover neuropsychological tests and behavioral measures (reaction time, accuracy) would not differ.

2. Methods

2.1. Subjects

Thirty healthy older female subjects (age between 60 and 79 years) were recruited through the Successful Aging Program. None of them had a history of epilepsy, head trauma, or major psychiatric condition. Generic determination of ApoE allelic status for the subjects was performed by polymerase chain reaction–restriction fragment length polymorphism (PCR-RFLP) (Black et al., 1990). The genotypes of 30 subjects were classified into 10 ApoE ε3/ε 4, 18 ApoE ε3/ε3, and 2 ApoE ε2/ε3. Subjects were divided into two groups based on the presence of the ApoE ε4 allele (ApoE ε4 carriers, $n = 10$; ApoE ε4 non-carriers, $n = 20$). First-degree family history of Alzheimer's disease was reported in two ApoE ε4 carriers and four non-carriers. Demographic information for the two groups of subjects is summarized in Table 1. There were no significant differences between ApoE ε4 carriers and non-carriers in age or educational level. All subjects signed informed consent forms, and the study was performed in accordance with a protocol approved by the UCI institutional review board.

2.2. Neuropsychological tests

All subjects received neuropsychological test battery to evaluate cognitive status and function. The battery included the Mini-Mental State examination as a screen for dementia (Folstein et al., 1975), WMS-III Logical Memory subtest (Wechsler, 1997) and the CERAD Word List Learning Task (Morris et al., 1989) to quantify episodic memory function, the 30-item Boston Naming Test (Kaplan et al., 1983), CERAD Animal Naming (Morris et al., 1989), and Controlled Oral Word Association (FAS Fluency) (Spreen and Benton, 1977) for language functions, the WAIS-III Block Design test (Wechsler, 1981) and CERAD Constructional Praxis test (Morris et al., 1989) for visual-spatial functions, and Trailmaking Test A and B (Reitan, 1958) for attention and executive function.

2.3. Study design

Subjects performed a target detection task by listening to a sequence of tones having a constant inter-stimulus interval of 2.5 s. Tones were presented from two speakers placed ∼0.75 m in front of the subject (70 dB SPL, 100 ms duration, 5 ms rise/fall times). A PC-based Neuroscan Stim1 system was used to generate and control the presentation of stimuli. Pure tones were either 1000 Hz "non-targets" or 2000 Hz "targets" and all subjects were able to clearly discriminate the auditory stimuli. Audiograms were performed on a minority of subjects (ApoE ε4 carriers = 3, ApoE ε4 non-carriers = 6) and showed, on average, normal to mild hearing loss (ApoE ε4 carriers = ∼20 dB, ApoE ε4 non-carriers = ∼25 dB) at the frequencies of the tones used for the target detection task (1000, 2000 Hz). Probability of presentation was 0.80 for non-targets and 0.20 for target tones (300 tones total). Subjects were instructed to listen to the tones and quickly, but accurately, press a button with the thumb of their dominant hand in response to targets. The sequence of tones was randomly determined except for the restrictions that two targets were never presented in a row, and a maximum of nine non-targets could be presented in a row.

2.4. Event-related potential recordings

Subjects were seated inside a sound attenuating, electrically shielded chamber. Depending on the subject, between 8 and 10 Ag/AgCl recording electrodes were placed on the scalp according to the 10/20 system (Jasper, 1958). All subjects had electrodes at Fz, Cz, Pz, C3 and C4 sites. Electrode impedances were <5 kΩ. Two electrodes were placed above and below the left eye to monitor eye movements, and one electrode was placed on the forehead to serve as the ground. Reference electrodes were placed on the left and right mastoid in a linked mastoid configuration. A PC-based Neuroscan recording system (Scan) with SynAmps (biological amplifiers) was used to sample and gather the EEG and EOG data. The EEG and EOG were digitally amplified (DC – 100 Hz,

sample rate = 500 Hz). Electrophysiological (EEG, EOG) and behavioral data were collected continuously, with additional off-line processing and analysis. An eyeblink algorithm was used to correct for such artifacts. Individual sweeps were then sorted and averaged according to stimulus type (non-target or target). Sweeps to targets were visually inspected for artifacts before being accepted into the average. Sweeps to non-targets were automatically rejected if the voltage on any electrode site exceeded 75 μV.

2.5. Data analysis

Reaction times were calculated relative to stimulus onset. Median reaction times were used to limit the influence of any outlier reaction times. Accuracy was the percent of correct responses to target tones (out of 60).

Event-related potentials were digitally filtered using FFT and inverse FFT procedures (DC – 30 Hz, 12 dB/octave). Amplitudes of event-related potentials were defined relative to 100 ms baseline period immediately before stimulus presentation, and latencies were defined relative to stimulus onset. Although the P50, N100, and P200 are present for both targets and non-targets, non-targets were analyzed alone because they were presented more often than targets, which improve measurement reliability. The N200 and P300 were measured to targets. The P50 component was defined as the maximum positivity between 40 and 70 ms post-stimulus, N100 was the maximum negativity between 90 and 130 ms, and the P200 was the maximum positivity between 150 and 210 ms. The N200 component was defined as the maximum negativity between 175 and 300 ms that immediately preceded the P300, which was the maximum positivity between 300 and 460 ms.

2.6. Statistical analysis

The ApoE groups (ε4 carriers, ε4 non-carriers) were compared on neuropsychological test scores, behavior, and event-related potentials in the target detection task using analysis of variance (ANOVA). p Values of <0.05 were considered significant. The purpose of this study is to define cortical potential changes associated with ApoE ε4 in normal aging, and we analyzed each potential at the scalp electrode site with the highest amplitude. For example, the P50, N100, P200, and N200 components were measured from the Cz site, and P300 measures were taken from the Pz site.

3. Results

3.1. Neuropsychological measures

Neuropsychological results from ApoE ε4 carriers and non-carriers are shown in Table 2. All subjects performed within the normal ranges, and there were no significant differences between the groups.

Table 2
Neuropsychological test results[a].

	ApoE ε4 carriers (n = 10)	ApoE ε4 non-carriers (n = 20)
MMSE score	29.8 ± 0.6	29.3 ± 0.9
WMS-III Logical Memory		
Immediate recall (SS)	14.1 ± 2.2	13.7 ± 2.3
Delayed recall (SS)	14.6 ± 3.2	14.2 ± 2.1
CERAD Word List		
Sum of trials 1–3	22.6 ± 4.2	23.8 ± 2.7
5 min delayed recall	8.1 ± 1.3	8.2 ± 1.9
30 min delayed recall	7.2 ± 2.6	8.5 ± 1.3
5 min delayed recognition	20.0 ± 0	19.8 ± 0.5
30 min delayed recognition	19.7 ± 0.7	19.8 ± 0.5
Boston Naming Test	27.9 ± 2.0	28.6 ± 1.6
CERAD Animal Naming	22.8 ± 5.1	22.9 ± 4.9
FAS Verbal Fluency (SS)	11.3 ± 1.8	12.5 ± 2.9
WAIS-III Block Design (SS)	10.8 ± 0.4	11.6 ± 2.7
CERAD Constructional Praxis	11.6 ± 2.1	10.6 ± 1.1
Trailmaking Test A (SS)	11.9 ± 2.3	12.1 ± 3.7
Trailmaking Test B (SS)	11.3 ± 1.5	11.4 ± 3.5

[a] Neuropsychological results reported as raw scores except for WAIS-III Logical memory, FAS Verbal Fluency, WAIS-III Block Design, and Trailmaking A and B that used age- or age and education-adjusted scaled scores (indicated by SS). Values are means ± standard deviations.

3.2. Behavioral data

There were no significant group differences in accuracy (ApoE ε4 carriers = 99%, ApoE ε4 non-carriers = 96%) and reaction time (p < 0.4; ApoE ε4 carriers = 399 ms, ApoE ε4 non-carriers = 363 ms).

3.3. Auditory cortical potentials

Auditory event-related potentials to non-targets and targets are shown for ApoE ε4 carriers and non-carriers in Fig. 1A and B. Individual amplitudes and latencies of the P300 are plotted in Fig. 1C and D for ApoE ε4 carriers and non-carriers.

3.3.1. Non-targets

There were no significant group differences in the amplitude or latency of P50, N100, and P200 components.

3.3.2. Targets

The N200 component was not analyzed because four subjects from each group did not have a clear N200 component. There was a significant group difference in the amplitude of the P300 component ($F_{(1,28)} = 6.4$; $p < 0.02$) with smaller amplitude in ApoE ε4 carriers than non-carriers. P300 latency was significantly longer in ApoE ε4 carriers compared to non-carriers ($F_{(1,28)} = 7.0$; $p < 0.02$).

Fig. 1C shows that 80% of the ApoE ε4 carriers had P300 amplitudes that were below the mean of non-carriers. Similarly, for P300 latency 80% of the ApoE ε4 carriers had

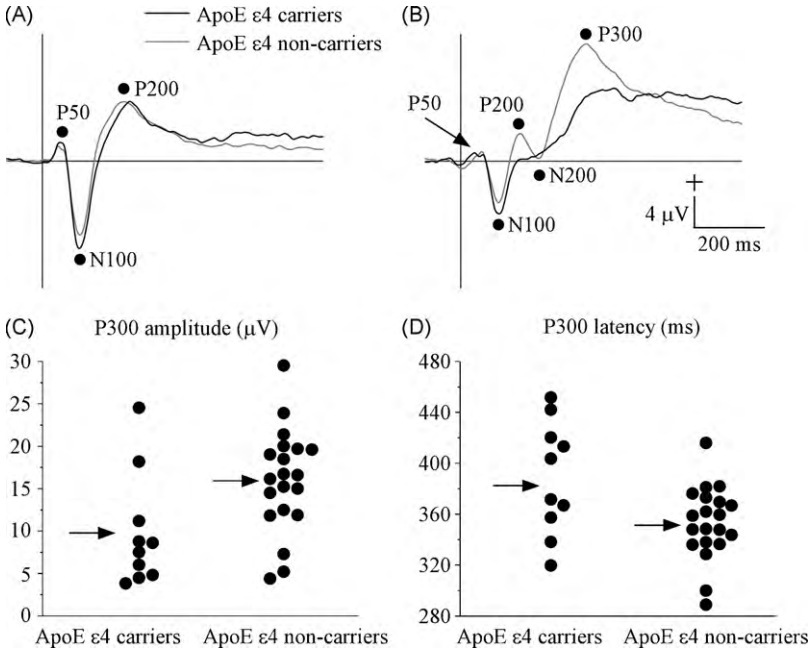

Fig. 1. Event-related potentials to (A) non-targets and (B) targets for healthy older female ApoE ε4 carriers and ApoE ε4 non-carriers and plots from individual 10 ApoE ε4 carriers and 20 ApoE ε4 non-carriers for (C) P300 amplitude and (D) P300 latency to targets. Averaged potentials were measured from Cz for P50, N100 and P200 components and Pz for N200 and P300 components and were low pass filtered (DC – 30 Hz). The vertical lines for (A) and (B) indicate stimulus onset, and the epoch lasts from −100 ms to 800 ms relative to the stimulus onset. Arrows in (C) and (D) indicate mean values for ApoE ε4 carriers and non-carriers.

P300 latencies that were above the mean of non-carriers (Fig. 1D). Specifically, four ApoE ε4 carriers and one non-carrier had P300 latencies that were 2S.D. above the mean of the non-carrier group. The greater likelihood of abnormal P300 latency (>2S.D.) observed in ApoE ε4 carriers was supported by a significant 2×2 χ^2 test of ApoE status (ApoE ε4 carriers, ApoE ε4 non-carriers) and P300 latency (abnormal, normal) ($\chi^2 = 5.9$, $p < 0.02$). There were no significant correlations between P300 amplitude and P300 latency within the groups of ApoE ε4 carriers ($r = 0.5$) and non-carriers ($r = 0.02$).

4. Discussion

The results of the present study show that an auditory sensory cortical component (P50) during the target detection task did not differ between ApoE ε4 carriers and non-carriers. In contrast, the auditory cognitive P300 component was significantly decreased in amplitude and prolonged in latency in ApoE ε4 carriers compared to non-carriers. Behavioral (reaction time, accuracy) and neuropsychological measures were comparable between ApoE ε4 carriers and non-carriers.

4.1. Auditory cortical sensory potential

The finding of normal P50 in ApoE ε4 carriers contradicts our hypothesis that ApoE ε4 carriers would show abnormally increased amplitude of sensory cortical response. We considered this hypothesis because P50 amplitude increases with normal aging and shows further increases in amnestic mild cognitive impairment that often anticipate the development of AD (Irimajiri et al., 2005; Golob et al., 2007). Amnestic mild cognitive impairment subjects that subsequently converted to AD had significantly larger P50 amplitudes than amnestic mild cognitive impairment subjects who remained stable (Golob et al., 2007). However, all of these immediately preceding studies were done without consideration of ApoE status. We suggest that ApoE status should be considered in future analyses of neural measures of normal aging.

Previous studies comparing passive listening of frequent ("standards") and infrequent ("deviant") stimuli have identified a component called the mismatch negativity (MMN: Näätänen et al., 1978, 2001, review). The MMN is evident ∼100–250 ms after stimulus presentation, and is more negative to deviant stimuli. The MMN shows little change with age when deviants are defined by changes in non-temporal features, such as frequency or intensity, but is attenuated when deviants are based on temporal features such as stimulus duration (Kisley et al., 2005).

The present study was not designed to record the MMN, as the goals were to define sensory and cognitive processing during active performance of a task, rather than passive listening which is often used for MMN studies. The interstimulus interval was also longer relative to many MMN studies (2.5 s vs. ≤∼1.0 s), and the probability of targets was somewhat higher ($p = 0.20$ vs. ∼0.10). Thus, the present study was not optimized for MMN recording, and indeed, a

clear MMN component was not always evident for individual subject data. One study has examined MMN amplitude as a function of ApoE4 genotype in older subjects having either objective or self-reported memory deficits, and found no significant MMN differences among ApoE genotypes (Reinvang et al., 2005). Future studies would be required to examine the MMN in older subjects without memory deficits beyond those expected for their age.

4.2. Auditory cortical cognitive potential

P300 latency gradually becomes longer with age (Goodin et al., 1978), and has additional prolongation in dementia as well as amnestic mild cognitive impairment (Golob et al., 2007). The results of the present study extend these earlier findings and show that P300 amplitude and latency distinguished female ApoE ε4 carriers from non-carriers. Differences in P300 latency among ApoE genotypes have also been observed in middle aged subjects with a family history of AD, but the effect of gender was not assessed (Green and Levey, 1999). Latency of the P300 has been suggested to reflect speed of cognitive processes underlying stimulus classification and memory updating (Donchin and Coles, 1988). Intracranial recording studies show that the P300 component is generated by widespread cortical systems involving parietal, temporal, and prefrontal cortex (Halgren et al., 1998).

The abnormal P300 responses found in ApoE ε4 carriers may be related to functional changes in temporal and parietal cortex, regions that exhibit AD pathology early in the disease process (Price and Morris, 1999). Positron emission tomography (PET) studies have shown that cognitively intact younger (20–39 years) and middle aged (50–65 years) ApoE ε4 carriers have a significantly reduced rate of glucose metabolism in parietal, temporal and prefrontal regions compared to non-carriers (Reiman et al., 1996, 2001; Smith et al., 1999). fMRI studies have also reported ApoE ε4 related differences in activation during a memory task in prefrontal, temporal, and parietal regions that contribute to the P300 (Bookheimer et al., 2000). Moreover, these same areas exhibit hypometabolism (Frackowiak et al., 1981; Alexander et al., 2002), reduced functional activity (Bäckman et al., 1999), and reduced EEG activity in the alpha band (Babiloni et al., 2006) in AD. Functional abnormality and hypometabolism in the parietal cortex are also reported to predict cognitive decline in non-demented older ApoE ε4 carriers (Small et al., 2000; Lind et al., 2006). Taken together, postmortem, neuroimaging, and the present ERP findings show that in subjects at heightened risk of AD cortical dysfunction is present without notable cognitive deficits.

It is of interest that four out of 10 ApoE ε4 carriers had abnormally prolonged P300 latency (>2S.D.) compared to one out of 20 non-carriers. The same pattern of abnormal P300 latencies was evident when the current results were compared with prior normative values for each subject's age that did not consider gender or ApoE status (Goodin et al., 1978). Neuropsychological measures of the five subjects with prolonged P300 latencies were generally in the middle range of all subjects in this study, and did not differ from clinical norms. Thus, the finding of increased incidence of abnormally delayed P300 potentials in ApoE ε4 carriers when clinical measures of cognitive function are normal may be relevant for identifying individuals who are particularly likely to develop cognitive decline and AD.

The present results showed neurophysiological changes that occur prior to the appearance of clinical abnormalities. Further studies would be necessary to show that these physiological changes are truly presymptomatic in a large population of normal older controls at risk for developing AD. Additionally, it would be useful to determine if P300 amplitudes and latencies change with ApoE status in young females, and if the level of task demand differentially affects sensory (P50) and behavioral responses (reaction times, accuracy) in ApoE ε4 carriers.

4.3. Summary

Possession of the ApoE ε4 allele is accompanied by normal sensory (P50) but abnormal cognitive (P300) cortical responses in healthy older females. Auditory cognitive P300 potentials may be sensitive to ApoE ε4-related neuronal abnormalities occurring prior to the clinical expression of memory or cognitive disorders accompanying mild cognitive impairment or AD.

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