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Cortical thickness is associated with different apolipoprotein E genotypes in healthy elderly adults

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ABSTRACT

Previous studies have consistently suggested that the ε4 allele of apolipoprotein E (APOE) gene is a major risk factor for Alzheimer's disease (AD). However, whether the ε2 allele, a possible protective factor for AD, will express its protective effect in terms of cortical thickness in healthy elderly carriers is unclear. The goal of this study is to clarify the effects of APOE genotypes on cortical thickness in nondemented elderly subjects. We used 164 healthy, cognitively normal, elderly subjects, who were grouped into ε2 carriers, ε3 homozygotes, and ε4 carriers respectively. The APOE ε2 carriers had a significant thicker (corrected $p < 0.05$) cortical thickness in the superior temporal cortex compared with the ε3 homozygotes. In addition to this area, the APOE ε2 carriers had a significantly thicker region in the dorsolateral prefrontal cortex (corrected $p < 0.05$) than did the ε4 carriers. These findings suggest that the different alleles of the APOE gene have distinct neuroanatomic effects in elderly healthy subjects and may play specific roles in the development of AD.

Alzheimer's disease (AD), the most common neurocognitive disorder, is characterized by a progressive loss of neurons and synapses, with cerebral deposits of amyloid-β (Aβ) senile plaques [21] and neurofibrillary tangles (NFTs) [18]. The apolipoprotein E (APOE) polymorphism, specifically the ε4 allele, is widely accepted as the most robust genetic risk factor for late onset Alzheimer's disease (LOAD) [4,33]. APOE ε4 has been reported as being related to a lower level of $A\beta_{42}$ in normal elderly adults [25,28] and a high level of tau in AD [17,34,35]. Both of these appear to contribute to the development of AD [20,31].

A growing number of studies have indicated that APOE ε4 modulates brain morphology specifically by a loss in hippocampal volume [6,24,29] and by causing abnormal white matter integrity [27]. The correlation between APOE ε4 and cortical thickness has also been increasingly reported. For example, healthy adults with the ε4 allele showed age-related reductions in cortical thickness in the medial prefrontal and pericentral cortex [9]. Thinner cortical thickness was also observed in the entorhinal cortex and the subiculum in healthy adults who had the ε4 allele [2].

Just as the APOE ε4 allele has been identified as a major risk factor for LOAD, other studies have found that the ε2 allele may have some protective qualities, since carriers appear to have a lower risk of developing Alzheimer's disease [10,37]. One study [32] observed increased cortical thickness in healthy children and adolescents who were ε2 carriers. Other researchers [6], however, did not find any effect of ε2 on brain volume in healthy elderly subjects.

Since APOE has been identified as major risk factor in LOAD, finding the effects of this gene on cortical thickness in elderly adults is important. Our goal was, therefore, to examine the cortical thickness across the entire cortex of healthy, elderly adults to see if it correlates with the various APOE genotypes, especially with the ε2 allele. We expected that we would find increased cortical thickness for the ε2 allele carriers and decreased cortical thickness for the ε4 allele carriers, each compared to the ε3 homozygotes.

Data used in this article were obtained from the *Alzheimer's Disease Neuroimaging Initiative* (*ADNI*) database (www.loni.ucla.edu/ADNI). The initial goal of ADNI was to recruit 800 adults, ages 55–90, to participate in the research—approximately 200 cognitively normal older individuals to be followed for 3 years, 400 people with MCI to be followed for 3 years, and 200 people with

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Table 1
Sample demographic characteristics.

	Genotype			*p*-Value
	APOE $\varepsilon2^+$ ($n=21$)	APOE $\varepsilon3\varepsilon3$ ($n=103$)	APOE $\varepsilon4^+$ ($n=37$)	
Age (years)	74.45 ± 5.97	75.94 ± 5.06	75.83 ± 4.80	0.483[a]
Gender (f/m)	11/9	55/47	18/19	0.710[b]
Education (years)	14.2 ± 3.31	16.12 ± 2.80	16.16 ± 2.79	0.081[a]
MMSE[a]	28.51 ± 0.32	$28.6 \pm 4\ 0.21$	29.13 ± 0.91	0.170[a]
Race (Asian/African American/White)	0/3/18	1/7/95	1/0/36	0.222 [b]

f/m: female and male; MMSE: Mini Mental State Examination.
[a] The *p*-value was obtained by ANOVA.
[b] The *p*-value was obtained by Pearson Chi-square.

early AD to be followed for 2 years. For up-to-date information see www.adni-info.org.

Our downloaded data initially included 225 baseline NC scans. We excluded 5 subjects because they converted to MCI or AD in 36 months. To ensure the accuracy of the segmentation, we manually checked the interface between the grey matter and white matter as well as the one between the white matter and the cerebrospinal fluid (CSF), and on this basis excluded 46 additional subjects due to segmentation errors. The resulting data for the cortical thickness analysis included 164 healthy, cognitively normal, elderly subjects, all collected from ADNI sites. The individuals were grouped into $\varepsilon2$ carriers (21), $\varepsilon3$ homozygotes (103) and $\varepsilon4$ carriers (37), with $\varepsilon2\varepsilon4$ individuals excluded from consideration. The Mini Mental State Examination (MMSE) and the education level had also been recorded as baseline data. Sample characteristics are presented in Table 1. In addition, those individuals in this study group for whom an intact record of their CSF biomarkers, including total tau (t-tau), hyperphosphorylated tau (p-tau), and $A\beta_{42}$, was available were separately grouped into APOE $\varepsilon2$ carriers (14), $\varepsilon3$ homozygotes (50) and $\varepsilon4$ carriers (14).

The data sets included standard T1-weighted MR images acquired sagittally using volumetric 3D MPRAGE with 1.25 mm $\times$ 1.25 mm in-plane spatial resolution, TE = 3.9 ms, TR = 90 ms and 1.2 mm thick sagittal slices (8° flip angle). All of the images were obtained using 1.5 T scanners. The MRI scans were acquired at multiple sites using a GE, Siemens or Philips 1.5 T system. The images were preprocessed using a number of steps detailed on the ADNI website. This preprocessing was done to correct for differences across scanners used at various ADNI sites.

We processed each scan using FreeSurfer [5,12] (http://surfer.nmr.mgh.harvard.edu/) with its volume and surface pipeline. Starting with the segmentation of white matter and the tessellation of the grey/white matter boundary, an initial surface was obtained after an automated topological correction. We used this surface as the initial shape for a deformable model that was used to reconstruct the pial surface.

When all the surfaces had been reconstructed, the cortical thickness was computed. Each subject's cortical thickness was measured in native space [11]. Surface based registration [13] was used to construct an average template, and all the individual reconstructed cortical surfaces were aligned to it. The cortical thickness measurements at the interconnection between the two hemispheres were masked because there is very little grey matter there. Finally, we smoothed the thickness using a heat kernel [3] 30 mm wide to increase the signal-to-noise ratio and improve the ability to detect morphometric variations.

We performed an Analysis of Covariance (ANCOVA) using SPSS 13.0 statistical software to assess the effects of APOE genotypes on biomarker levels (tau, $A\beta_{42}$), controlling for age and gender. After that, a post hoc multiple comparison using Fisher's LSD was conducted when the ANCOVAs were significant. In all tests, results with probability values less than 0.05 were considered statistically significant.

We used SurfStat (http://www.math.mcgill.ca/keith/surfstat/) toolbox for Matlab (R2007a, The Mathworks, Natick, MA, USA) to perform statistical analyses of the cortical thicknesses. Statistical tests were performed at every unmasked point on the pial surface. To test for variability in the thickness of the cortex, we applied a general liner model to check point-wise thickness differences using the APOE genotypes as fixed factor, and age and gender as covariates. The ensuing *p*-values were adjusted for multiple comparisons on the cortical surface to control for the false positive rates by the random field theory [39]. We discarded statistically significant clusters containing fewer than 50 points, in order to reduce the possible influence of noise.

We tested the effects of the APOE genotypes on the CSF biomarkers t-tau, p-tau and $A\beta_{42}$ level on a smaller subset of 78 samples. The ANCOVA showed a significant effect of APOE on $A\beta_{42}$ level ($p < 10^{-4}$). In addition, a post hoc comparison showed a statistically significant stepwise trend toward lower $A\beta_{42}$ levels, with $\varepsilon2$ being the highest, $\varepsilon4$ the lowest, and $\varepsilon3$ homozygotes occupying an intermediate position ($p = 0.034$ for the step from $\varepsilon2$ to $\varepsilon3$, and $p < 10\,e{-}4$ for the one from $\varepsilon3$ to $\varepsilon4$) (Fig. 1). In contrast to $A\beta_{42}$, the effects of APOE on CSF t-tau or p-tau were only a trend ($p = 0.063$ and $p = 0.054$ respectively), and this was limited to comparisons of APOE $\varepsilon4$ and $\varepsilon2$ carriers ($p = 0.024$ for t-tau, and $p = 0.016$ for p-tau) (Fig. 1). No significant association between the APOE genotype and the MMSE score was observed ($p = 0.170$).

The results of the group comparisons of cortical thickness are displayed in Fig. 2. No increases, only decreases, in cortical thickness were found in any region in the APOE $\varepsilon4$ carriers and the $\varepsilon3$

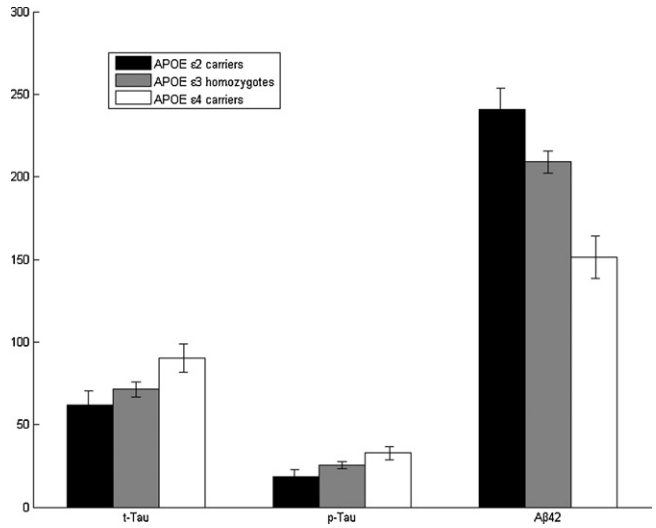

Fig. 1. Mean biomarker levels (t-tau, p-tau and Aβ42) for the APOE genotype groups. The APOE $\varepsilon2$ carriers are represented in black, the $\varepsilon3$ homozygotes in grey and the $\varepsilon4$ carriers in white. The CSF Aβ42 levels show a significant stepwise trend downward, from $\varepsilon2$ carriers to $\varepsilon3$ homozygotes to $\varepsilon4$ carriers; whereas the t-tau and the p-tau levels show the opposite trend.

homozygotes when compared with the same regions in the ε2 carriers. This was also true in the APOE ε4 carriers when they were compared with the ε3 homozygotes. The APOE ε2 allele carriers had significantly increased cortical thickness primarily in the bilateral superior temporal cortices, bilateral dorsolateral prefrontal cortices, left supramarginal gyrus, left precentral and postcentral gyri, left parietal operculum and right parahippocampal region compared to the APOE ε3ε3 subjects. The APOE ε2 carriers also had a significantly thicker cortex primarily in the bilateral lateral and medial frontal regions, the right parahippocampal cortex, right temporoparietal cortex and bilateral temporal regions than did subjects who were ε4 allele carriers. The APOE ε4 carriers showed significant atrophy in the left medial prefrontal cortex and left orbitofrontal cortices compared with the ε3 homozygotes. After performing multiple comparison corrections using random field theory, we determined that the APOE ε2 carriers had significantly thicker cortical thickness in the left superior temporal cortex compared with the ε3 homozygotes. Moreover, the cortices in the left superior temporal and left dorsolateral prefrontal region were thicker in the APOE ε2 carriers than in the ε4 carriers. However, no significant differences remained when comparing the APOE ε3 homozygotes with the ε4 carriers after applying the multiple comparison correction.

In this study, we used a surface-based approach to quantify the local cortical thickness in healthy nondemented adults with different APOE genotypes. We observed a stepwise lower $A\beta_{42}$ level for different APOE genotypes, and thicker cortical thickness when comparing APOE ε2 carriers to ε4 carriers or ε3 homozygotes in specific regions.

We examined the effect of APOE ε2 on brain morphology by comparing subjects with this genotype with ε3 homozygotes and ε4 carriers. Interestingly, when we compared the others with the ε2 carriers, the ε3 homozygotes and the ε4 carriers had a similar thinner cortical area, which was primarily located in the bilateral lateral prefrontal cortices, the bilateral temporal cortices, and the right parahippocampal region. The differences in the left superior temporal gyrus, which is associated with speech production [22,30], remained significant after a multiple comparison correction. A loss of the speech production function is a symptom in the development of AD [16]. Moreover, we observed a significant stepwise lowering of the $A\beta_{42}$ levels across the APOE genotypes and a significantly higher t-tau or p-tau level when comparing APOE ε2–ε4 carriers. Importantly, the accumulation of Aβ peptide and tau in neurons has been implicated in the development of AD [20,31]. Aβ peptide deposition [8] and neurofibrillary tangle development [36] have been found to occur early in the development of AD. Thus, the same

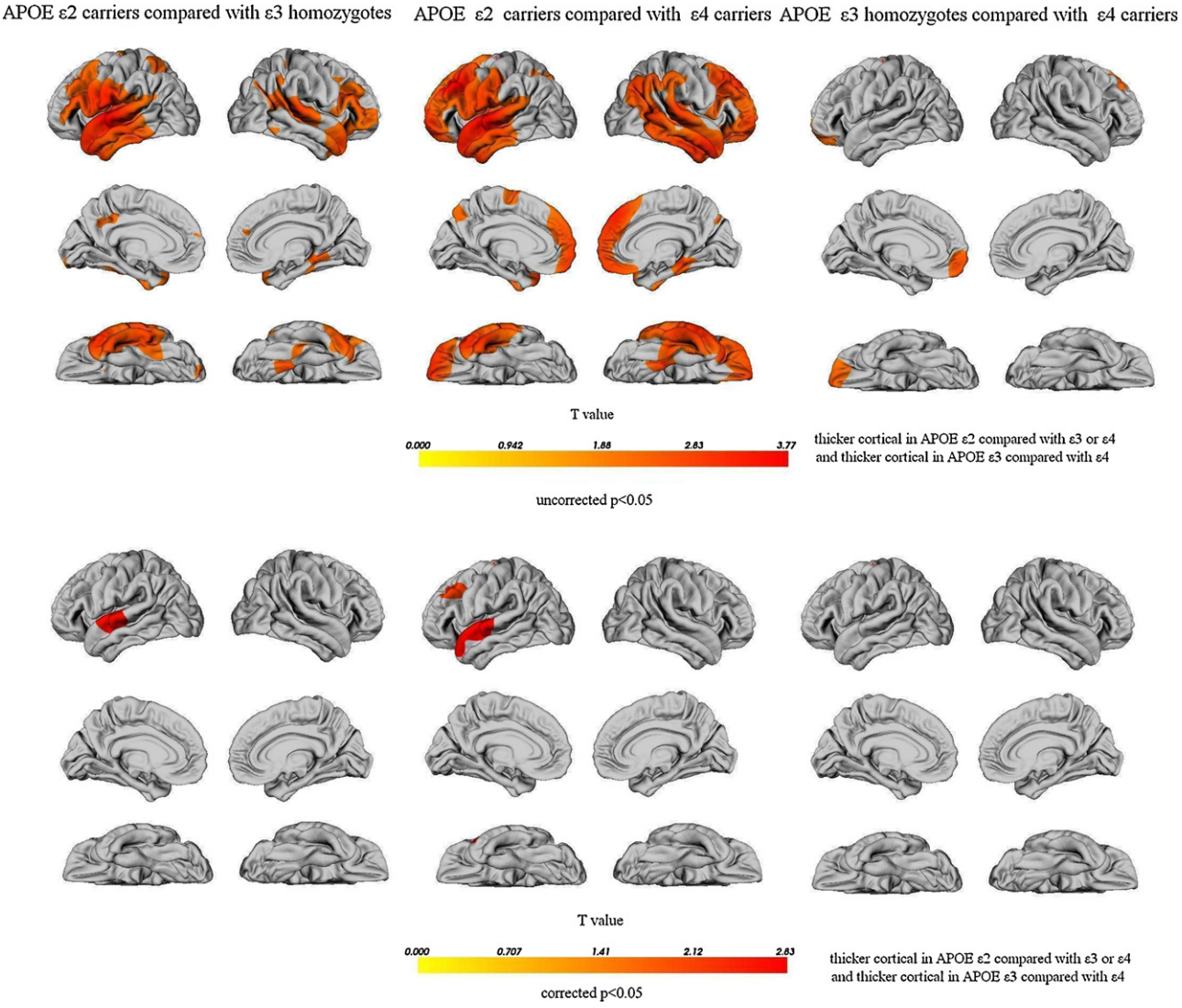

Fig. 2. Cortical thinning maps (in percentage). Only points with statistically significant differences ($p < 0.05$) are displayed. The top shows uncorrected $p < 0.05$, and the bottom shows $p < 0.05$ corrected. The color bar displays the T value of the cortical thickness differences in millimeters.

biological markers, that is, those for tau and $A\beta_{42}$, which contribute to the Aβ peptide and neurofibrillary tangles could also induce a metabolic decline leading to neuronal loss and thus perhaps cortical thinning [19].

In addition to thinning in the superior temporal cortex, the ε4 allele was associated with greater atrophy in the bilateral prefrontal cortex when compared with the ε2 allele. Moreover, after applying a multiple comparison correction, the differences in the left dorsolateral prefrontal cortex, which has been suggested as being correlated with cognition control [26] and long term memory formation [1], remained significant. Again, the failure of these functions is characteristics of AD [15]. Thus, we can conclude that the finding that APOE ε2 allele carriers possess a thicker left dorsolateral prefrontal cortex may indicate a specific protective role against possible memory loss in the development of AD.

We also found that APOE ε4 carriers displayed atrophy (uncorrected $p < 0.05$) in the left prefrontal cortex and the left orbitofrontal cortex compared to ε3 homozygotes. Although when comparing ε3 with ε4 individuals we did not observe atrophy in the parahippocampal cortex, which is the earliest region affected in AD [23], atrophy was present in this region in the ε3 homozygotes or ε4 carriers when compared with the APOE ε2 carriers (uncorrected $p < 0.05$). Published studies about APOE ε4s effect on brain morphology, especially in the parahippocampal region, are controversial. Several studies have suggested that APOE ε4 is related to hippocampal volume loss [6,24,29], but one recent study [29] which also used ADNI data found no effect of APOE ε4 on hippocampal volume loss in the normal control group. Because most published studies have subdivided APOE genotypes into APOE ε4 non-carriers and carriers, the inclusion of the ε2 carriers may have caused a continuum of thicknesses that caused any e4-related thinning of the parahippocampal cortex to be lost in the data.

The results of the present study may also indicate that APOE genotypes affect cognitive function in normal aging. A large meta-analysis study [38] investigated the effects of the APOE genotype on cognition in the nondemented population. Specifically, in the nondemented population the APOE ε4 allele carrier often had impaired cognitive functioning, and ε2 allele carriers showed better performance on episodic memory. Moreover, increased cortical thickness, including that in the frontal and temporal regions, was associated with higher cognitive performance in older healthy adults [14]. Our results are compatible with these findings. In this study, we did not find a significant relationship between the APOE genotypes and the MMSE scores. One of major reasons may be a ceiling effect that appeared because the healthy nondemented individuals had high scores that were similar to those of the subjects on these measures. However, in a previous study, APOE ε4 carriers were observed to have a greater rate of cognitive decline as shown by their MMSE scores using nondemented individuals [7]. Thus, the effects of APOE genotypes on cognitive decline in normal aging require further investigation.

In conclusion, the APOE ε2 allele may have a specific protective role in the development of AD. To our knowledge, this is the first study to explore the cortical thickness pattern between APOE genotypes in nondemented elderly subjects. Further studies are needed to clarify the exact mechanism and role of the APOE genotypes in the cognitive decline associated with normal aging as well as in the development of AD.

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