ELSEVIER

Neurobiology of Aging 33 (2012) 304–322

NEUROBIOLOGY OF AGING

www.elsevier.com/locate/neuaging

Apolipoprotein E ε4-related thickening of the cerebral cortex modulates selective attention

Thomas Espeseth[a,*], Lars T. Westlye[a], Kristine B. Walhovd[a], Anders M. Fjell[a], Tor Endestad[a], Helge Rootwelt[b], Ivar Reinvang[a]

[a] Center for the Study of Human Cognition, Department of Psychology, University of Oslo, Oslo, Norway
[b] Department of Medical Biochemistry, Rikshospitalet, University Hospital, Oslo, Norway

Received 28 February 2008; received in revised form 19 September 2009; accepted 27 December 2009

Abstract

APOE ε4 carriers have thicker cortex in several neocortical areas than ε4 noncarriers (Espeseth T., Westlye L.T., Fjell A.M., Walhovd K.B., Rootwelt H., Reinvang I., 2008. Accelerated age-related cortical thinning in healthy carriers of apolipoprotein E ε4. Neurobiol. Aging 29, 329–340). To investigate potential physiological and cognitive correlates of these anatomical effects structural magnetic resonance imaging (MRI) data were obtained from 20 *APOE* ε3 homozygotes and 20 ε4 hetero- and homozygotes, and event-related potentials (ERPs) were recorded during a selective attention task (i.e. three-stimulus oddball). Several areas in both hemispheres were thicker in ε4 carriers than in noncarriers. ε4 carriers also had lower amplitudes to distractors (P3a) and lower target detection accuracy than noncarriers. Mean thickness in cortical areas were correlated with P3a amplitudes, which in turn correlated with accuracy. Path analyses showed that *APOE*-related difference in accuracy was mediated by *APOE*-related differences in cortical thickness and P3a amplitudes. The results suggest that *APOE* ε4 modulates the structural integrity of critical nodes in brain attentional networks.

Keywords: *APOE*; Cognition; Event-related potentials; Genetics; Morphometry; P300; Selective attention

1. Introduction

Inheritance of the apolipoprotein E (APOE) ε4 genotype is associated with increased risk of developing Alzheimer's disease (AD) and younger age of AD onset (Corder et al., 1993; Raber et al., 2004). The ε4 allele has been associated with impaired repair mechanisms following lesions in animals and humans (Sundstrom et al., 2004; Teter et al., 2002), and a growing literature shows that APOE ε4 also modulates brain morphology in healthy participants, including white matter volume and integrity (Bartzokis et al., 2006; Espeseth et al., 2006; Nierenberg et al., 2005; Persson et al., 2006; Smith et al., 2008; but see Adamson et al., 2008; Cherbuin et al., 2008; Schmidt et al., 1996), hippocampal volume (Cohen et al., 2001; Den Heijer et al., 2002; Lemaître et al., 2005; Moffat et al., 2000; Plassman et al., 1997; but see Reiman et al., 1998; Schmidt et al., 1996), and amygdalar volume (Den Heijer et al., 2002). When significant differences are found, ε4 carriers are typically reported to have smaller volumes and reduced structural integrity. In recent reports from our own work on *APOE* and magnetic resonance imaging (MRI)-derived morphological measures (Espeseth et al., 2006, 2008), there was nonsignificant trends for lower total cortical and white matter volumes for ε4 carriers. ε4 carriers were also shown to have attentional deficits compared with noncarriers, and these effects were partly mediated by total white matter (WM) volume (Espeseth et al., 2006). However, in the same sample there were also a distributed set of cortical areas in which ε4 carriers had thicker cortex than noncarriers (Espeseth et al., 2008). Among these were bilateral prefrontal areas, the parahippocampal gyrus, and occipital and

* Corresponding author at: Center for the Study of Human Cognition, Department of Psychology, University of Oslo, Box 1094, Blindern, N-0317 Oslo, Norway. Tel.: +47 22845135.
E-mail address: thomas.espeseth@psykologi.uio.no. (T. Espeseth).

0197-4580/$ – see front matter © 2012 Elsevier Inc. All rights reserved.
doi:10.1016/j.neurobiolaging.2009.12.027

temporal regions. Potential physiological and cognitive correlates of these genotype-related differences, which would be important for the assessment of the functional significance of the differences in cortical thickness, were not investigated. Hypothetically, if the ε4-related cortical thickening is part of a dysfunctional process associated with the ε4 allele, one should expect a negative correlation between thickness in these areas and relevant physiological and cognitive processes. The purpose of the present study is to investigate this hypothesis directly, by identifying cortical areas where thickness is related to *APOE* status, and then test whether these cortical areas mediate effects of *APOE* on event-related potentials (ERPs) and behavioral accuracy and reaction time in a selective attention task (P3a/ P3b). To show how the variance can be explained across separate neurobiological levels, we make use of a path analysis approach based on structural equation modeling in which the causal relations between the variables are explicitly modeled.

In the human central nervous system apolipoprotein E (apoE) plays a key role in transport and metabolism of plasma cholesterol and triglycerides, and is involved in synaptogenesis, as well as maintenance and repair of neurons (Mahley et al., 2006; Mauch et al., 2001). Its gene locus at chromosome 19q13.2 (*APOE*, GenBank accession AF261279) includes a distributed set of intronic and exonic single-nucleotide polymorphisms (SNPs) (Nickerson et al., 2000) but more than 95% of the apolipoprotein E protein variation in Caucasians is attributable to only 2 SNPs (Gerdes et al., 1992). They give rise to *APOE* alleles ε2, ε3, and ε4, and their 3 corresponding isoforms of the protein (see Fig. 1 for details).

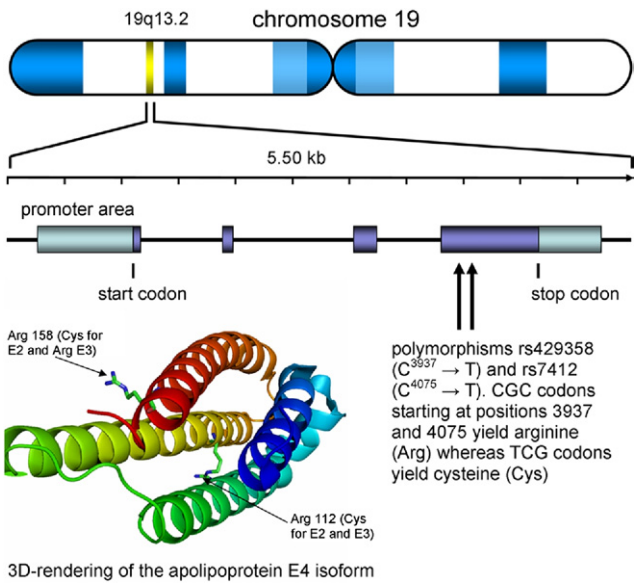

Fig. 1. Schematic illustration of chromosome 19 of the human genome. The golden area represents a 5.5 kilobase fraction of DNA at position 19q13.2 constituting the *APOE* gene, including promoter regions. The purple areas represent exons and the lines in between represent introns. The approximate positions of the 2 most well-known single-nucleotide polymorphisms (SNPs) are indicated by arrows. Positions are identified by genomic marker numbers as provided by Nickerson et al. (2000). The ε2 allele encodes the E2 isoform which contains cysteine at amino acid positions 112 and 158 (Cys^{112}–Cys^{158}), the ε3 allele encodes the E3 isoform (Arg^{112}–Cys^{158}), and the ε4 allele encodes the E4 isoform (Arg^{112}–Arg^{158}). Bottom left: Snapshot of a 3-dimensional rendering of the apolipoprotein E4 isoform. The 2 polymorphic sites are indicated by arrows. *APOE* ε4 carriers have arginine at both sites (amino acid 112 and 158), whereas non-carriers have cysteine at 1 or both sites.

APOE has been shown to influence a broad range of cognitive functions both in AD and normal aging (Bondi et al., 1995; Deary et al., 2002; Driscoll et al., 2005; Parasuraman et al., 2002; Rosen et al., 2002; Small et al., 2004; Wisdom et al., in press; but see Jorm et al., 2007; Luciano et al., 2009; Raz et al., 2009), including replicated findings of *APOE*-related modulation of attentional functions (Espeseth et al., 2006; Greenwood et al., 2000, 2005). Selective attention gives salient or task-relevant stimuli privileged access to limited capacity information processing systems and reduces interference from competing stimuli, and is dependent on the finely tuned coordination of activity generated by a distributed set of cortical and subcortical sites (Bundesen et al., 2005; Corbetta and Shulman, 2002; Desimone and Duncan, 1995; Knudsen, 2007; Mesulam et al., 2005; Posner and Petersen, 1990; Soltani and Knight, 2000). Two corticocortical neural systems are involved in controlling attentional deployment. Goal-directed attention is implemented by a bilateral dorsal frontoparietal network. Areas in the intraparietal sulcus and the superior parietal lobule, and a dorsal frontolateral area along the precentral gyrus near the frontal eye fields embody the critical nodes in this network. Goal-directed attention results from top-down signals sent from this network to sensory regions where they function to bias the competition for limited processing resources between sensory signals stimulating the same receptive fields of sensory neurons (Bundesen et al., 2005; Desimone and Duncan, 1995). A separate but partly overlapping right hemisphere system known as the ventral frontoparietal network includes the temporoparietal junction (defined as the intersection of the ventral part of the supramarginal gyrus, the posterior part of the superior temporal sulcus and gyrus, and the anterior part of the lateral occipital cortex), and regions in the ventral frontal cortex (parts of the middle frontal gyrus, the inferior frontal gyrus, frontal operculum and anterior insula). This system is not activated by goals or task-defined expectations but responds together with the dorsal system when expectations are violated by the detection of behaviorally relevant objects. For example, both systems are activated by the detection of invalidly cued targets in the Posner paradigm (Corbetta et al., 2000; Kincade et al., 2005; Macaluso et al., 2002; Vossel et al., 2006). In a letter discrimination version of the Posner cued spatial attention task (Parasuraman et al., 1992; Posner, 1980), *APOE* genotype has been shown to modulate selective attention in middle-aged and old healthy participants (Espes-

eth et al., 2006; Greenwood et al., 2000, 2005). In these studies, ε4 carriers were disproportionably penalized by invalid spatial cueing, probably reflecting deficient attentional reorienting.

Critically, both systems are also activated when objects appear infrequently as in oddball tasks (Bledowski et al., 2004; Braver et al., 2001; Corbetta et al., 2008; Halgren et al., 1998; Kiehl et al., 2001; Knight, 1984, 1996; Linden et al., 1999; Marois et al., 2000; Ranganath and Rainer, 2003; Soltani and Knight, 2000; Yamaguchi and Knight, 1991, 2004). Oddball task are among the most widely used attentional paradigms in ERP research. In the 3-stimulus version of this task, infrequent target and distractor stimuli and frequent standard stimuli are randomly intermixed and presented sequentially to subjects who are instructed to respond to target stimuli only. Typically, target stimulus processing elicits a centroparietal positivity known as the P3b component which peaks at about 300–600 ms after stimulus onset (Donchin and Coles, 1988). Infrequent distractors and also novel stimuli elicit a positive waveform at fronto-central scalp sites known as the P3a or novelty P3 (Courchesne et al., 1975). P3a and P3b have been proposed to be correlates of partly separate attentional processes. P3a is thought to reflect stimulus-driven distractor processing (i.e., transient signal-driven reorienting, Corbetta et al., 2008) when the target/standard discrimination is transiently interrupted by distractor stimuli. On this account, distractor encoding leads to a disengagement of attention from the task-relevant features and subsequent reallocation of attention toward the salient distractor stimuli (Bledowski et al., 2004a, 2004b; Linden, 2005). P3b is considered to reflect top-down processes related to voluntary attention and working memory. In particular, P3b is thought to reflect the "template-matching" process occurring when an external stimulus is matched to the internally represented target template (Soltani and Knight, 2000). It is suggested that target detection predominantly involves retrieval processes while the detection of salient distractors engage working memory updating (Bledowski et al., 2004a).

Event-related functional MRI (fMRI) has shown that in contrast to standard stimuli, novel or distractor stimuli activate the superior and middle frontal gyri, the cingulate gyrus, the precuneus and inferior and superior parts of the parietal lobes, middle temporal gyrus, the cuneus and fusiform gyrus, and the hippocampus (Bledowski et al., 2004; Braver et al., 2001; Corbetta et al., 2008; Kiehl et al., 2001; Linden et al., 1999; Marois et al., 2000; Ranganath and Rainer, 2003; Yamaguchi et al., 2004). Target stimuli activate many of the same areas but several motor-related regions, the supramarginal gyrus, thalamus, caudate nucleus, and insula were preferentially activated in target trials (Yamaguchi et al., 2004). A recent morphometric study including an old age sample (mean age 70 years), and involving MRI protocols and ERP paradigms similar to those used in the present study, showed a positive correlation between thickness in a set of cortical areas (i.e., middle and inferior frontal gyri, superior parietal lobes, the temporoparietal junction [TPJ] and the posterior cingulate) and P3a amplitude (Fjell et al., 2007). P3b amplitude was not significantly related to cortical thickness in this sample. Thus, intracranial ERP (Halgren et al., 1998), fMRI and MRI-based morphometry converge fairly well on identifying a distributed but limited set of cortical areas for the generation of P3a and P3b components. Notably, bilateral prefrontal, parietal and temporoparietal, and hippocampal areas seem to be particularly important for the generation of P3.

Accumulating evidence suggests that attention selectively synchronizes the rhythmic responses of neurons that are tuned to the spatial and feature attributes of the attended sensory input at a local level, and also regulates which locally synchronized neuronal groups phase-synchronize their rhythmic activity across long-range connections (Siegel et al., 2008; Womelsdorf and Fries, 2007; Womelsdorf et al., 2006). Because the strength of synchronization is functionally related to perceptual accuracy and behavioral efficiency, relatively small changes in structural integrity in this highly interconnected network may therefore alter attentional function, and more generally, cognitive function and mental health (Uhlhaas and Singer, 2006). Possibly, *APOE*-related effects on attentional functions may be mediated by brain changes detectable by magnetic resonance imaging and accompanying brain activity changes detectable by ERP. Consistent with this assumption, several studies have demonstrated correlations between regionally specific cortical thickness and cognitive functions associated with these regions (Dickerson et al., 2008; Fjell et al., 2006; Makris et al., 2007; Narr et al., 2007; Shaw et al., 2006; Sowell et al., 2008; Walhovd et al., 2006).

Although significant effects of *APOE* genotype have been obtained with relatively small samples (total $n \sim 100–200$) in behavioral studies (Espeseth et al., 2006; Greenwood et al., 2000, 2005), penetrance of genetic polymorphisms could be even greater for physiological rather than for behavioral functional measures (Goldberg and Weinberger, 2004). Thus, direct physiological indexes of attention, such as ERPs that are directly generated by the activity of neuronal assemblies, are probably more sensitive to variability in cortical thickness than behavioral measures. Electrophysiological studies (i.e., electroencephalogram [EEG] and ERP) have demonstrated that in persons at familial risk for AD, and patients with mild cognitive impairment (MCI) and mild AD, ε4 carriers have reduced resting-state α-frequency power (Babiloni et al., 2006; Ponomareva et al., 2008), and lower amplitudes in auditory ERPs (Green and Levey, 1999; Reinvang et al., 2005).

In the present study, structural MRI scans and ERP data were obtained from 40 healthy persons aged 48–75 years of whom half were carriers of at least 1 ε4 allele and half were ε3 homozygotes. Genotype groups were statistically well-

Table 1
Group demographic characteristics, means and standard deviations of estimated full-scale IQ (WASI) and raw scores on selected neuropsychological tests

Variable	Genotype				p[a]
	APOE ε4+		*APOE* ε4−		
	n	Mean (SD)	*n*	Mean (SD)	
Participants (n = 40)	20		20		
Male/female	13/7		15/5		0.49
Age		61.5 (8.2)		63.2 (8.2)	0.50
Education		14.4 (2.6)		14.6 (2.9)	0.82
WASI		123.5 (11.5)		121.1 (9.7)	0.49
Stroop CW		59.8 (20.8)		57.4 (12.0)	0.66
TMT A		35.5 (13.8)		37.1 (13.9)	0.73
TMT B		74.0 (29.1)		74.3 (25.1)	0.97
Digit-symbol		52.6 (13.1)		52.3 (9.4)	0.95
CVLT 1–5 total		58.1 (13.3)		50.9 (10.3)	0.06
CVLT long delay		13.7 (2.5)		11.7 (2.7)	0.02

Digit-symbol from WAIS-R. CVLT 1–5 total = total score on trial 1 through 5. CVLT long delay = Score on 30-minute delay recall.
Key: WAIS-R, Wechsler Adult Intelligence Scale-Revised; CVLT, California Verbal Learning Test; Stroop CW, Stroop color-word conflict; TMT A and B, Trail Making Test part A and B; WASI, Wechsler Abbreviated Scale of Intelligence.
[a] p-values are 2-tailed and based on independent samples t tests with *APOE* genotype as grouping variable.

matched on demographic and neuropsychological measures except for better delayed verbal memory scores for ε4 carriers on California Verbal Learning Test (CVLT)-II (see Methods and Table 1). The effect of *APOE* genotype on cerebral cortical thickness was first tested on a point-by-point basis across the entire cortical mantle. We then identified regions where *APOE* genotype affected cortical thickness and asked if *APOE*-related differences in cortical thickness mediated *APOE*-related changes in P3a and P3b amplitudes and task performance. The present sample was a subsample extracted from the sample used in Espeseth et al. (2008), excluding ε2 carriers. We expected to replicate the *APOE*-related differences in cortical thickness reported there with this smaller sample. Based on the assumption that attentional reorienting is an underlying computational component in both distractor processing in the oddball task and processing of invalidly cued targets in the cued spatial attention task, we predicted that ε4 carriers might have attenuated P3a amplitudes. We finally hypothesized that genotype would be associated with thicker cortex in attentional networks and that regions with thicker cortex in ε4 carriers would correlate negatively with ERP amplitudes and behavioral accuracy.

2. Methods

2.1. Participants

An initial sample of 42 persons with ages ranging from 48 to 75 years were included. Two participants were subsequently excluded from analysis (1 missing MRI, 1 with high error rate in the ERP paradigm), leaving 40 complete datasets. Participants were recruited through advertisements in local newspapers. Candidates were first interviewed by phone according to a check list about health and previous illness or injuries. Exclusion criteria were previously diagnosed neurological or psychiatric illness, any other chronic illness that might influence test performance, or sensory or motor impairments. Participants with a history of alcohol or substance abuse, or present addictive disorders, were also excluded. Participants had to be native speakers of Norwegian and have completed obligatory basic education (7 years for this age group) without diagnosed reading or learning disorders. Persons using adequate medication for hypertension, diabetes, or hypercholesterolemia were not excluded. Participants were not allowed to consume nicotine or caffeine during the test period or in the laboratory premises, but were not required to abstain from these substances before attendance. The groups were selected from a larger sample (see Espeseth et al., 2006) on the basis of having a balanced frequency of the *APOE* alleles (50% with ε4, no participants with ε2). All Participants completed Beck's Depression Inventory (BDI) as a measure of the presence of symptoms of depression. The range of scores was 1–12, well below the lower cutoff for presence of mild depression. Mean scores were 5.2 and 4.8 for ε4 carriers and noncarriers, respectively. The difference was not statistically significant (p = 0.67). The Vocabulary and Matrix reasoning subscales of the Wechsler Abbreviated Scale of Intelligence (WASI, Wechsler, 1999) were used to estimate IQ. Furthermore, we used tests of psychomotor speed, attention, and executive functions [Trail Making A and B, Wechsler Adult Intelligence Scale-Revised (WAIS-R) Digit Symbol, Delis-Kaplan Executive Function System (D-KEFS) Stroop Color Word (Delis et al., 2001)], and of memory [California Verbal Learning Test II (CVLT-II; Delis et al., 2000)]. Table 1 summarizes the participants' demographic and neuropsychological characteristics. There was no significant age, sex, IQ, or neuropsychological differences between genotype groups except significantly better delayed recall scores on CVLT-II for ε4 carriers.

All participants read an information sheet and signed a statement of informed consent approved by the regional ethical committee for medical research. Permission to obtain and store blood samples for genotyping together with phenotype data in a biobank was given by the Department of Health, and permission to establish a registry with relevant information for a time period of 10 years was given by the Department of Health.

2.2. DNA extraction and genotyping

Genotyping was performed by real-time polymerase chain reaction (PCR) with allele-specific fluorescence energy transfer probes and melting curve analyses on the LightCycler™ system (Roche Diagnostics, Mannheim, Germany). DNA was extracted from 300 μL whole blood using Magna Pure LC DNA Isolation Kit – Large Volume on the

Magna Pure LC (Roche Applied Science, Indianapolis, IN), eluted and diluted to 1 mL, of which 5 μL was applied in each assay.

Typing of the *APOE* ε2, ε3 and ε4 genotypes was performed using the LightCycler APOE Mutation Detection Kit (Roche Diganostics). The assay was performed as specified by the supplier, except for scaling down the total assay volume from 20 μL to 10 μL. The laboratory participates in an external quality assurance program (Equalis, Uppsala, Sweden) that includes APOE genotyping.

2.3. Mri protocol and volumetric analysis

A Siemens sonata 1.5 Tesla magnet (Siemens, Erlangen, Germany) with a conventional head coil was used. Two 3-dimensional magnetization prepared rapid gradient echo (MP-rage) T_1-weighted sequences, each 8 minutes and 46 seconds, were run for all participants. Each volume consisted of 128 sagittal slices (1.33 × 1 × 1 mm), with an in-plane voxel size of 1 mm^3 and were acquired with repetiton time (TR) = 2730 ms, echo time (TE) = 3.43 ms, inversion time (TI) = 1000 ms, flip angle = 7°, and 256 × 256 matrix. All morphometric analyses were done with the FreeSurfer software (surfer.nmr.mgh.harvard.edu/fswiki). Total brain volume was estimated using the procedures described by Fischl et al. (2002). This procedure automatically assigns a neuroanatomical label to each voxel in an MRI volume based on probabilistic information automatically estimated from a manually labeled training set. Intracranial volume (ICV) was computed using the procedure specified by Buckner et al. (2004). The procedures for automatic volumetric measurement of the cortical mantle are described by Salat et al. (2004). Cortical thickness measurements were obtained by reconstructing representations of the gray/WM boundary (Dale and Sereno, 1993; Dale et al., 1999) and the cortical surface and then calculating the distance between those surfaces at each point across the cortex. Cortical thickness was measured in native space. This method uses both intensity and continuity information from the entire 3-dimensional magnetic resonance (MR) volume in segmentation and deformation procedures to construct representations of cortical thickness. The maps are created using spatial intensity gradients across tissue classes and are therefore not simply reliant on absolute signal intensity. As the maps are not restricted to the voxel resolution of the original data, submillimeter differences between groups can be detected (Fischl and Dale, 2000). Thickness measures are mapped onto the inflated surface of each participant's reconstructed brain (Dale and Sereno, 1993; Fischl et al., 1999), thus allowing visualization without interference from cortical folding. Maps were smoothed using a circularly symmetric Gaussian kernel across the surface with a standard deviation of 12.6 mm and averaged across participants using a nonrigid high-dimensional spherical averaging method to align cortical folding patterns (Fischl et al., 1999). This procedure provides accurate matching of morphologically homologous cortical locations among participants on the basis of each individual's anatomy while minimizing metric distortions, resulting in a mean measure of cortical thickness for each group at each point on the reconstructed surface. The methodology for morphometric analysis has been validated with histological (Rosas et al., 2002) and manual measurement (Kuperberg et al., 2003). Regional WM volume calculation and parcellation depends on the preceding cortical parcellation in which the cortex was divided into 33 different gyral-based areas in each hemisphere by use of an automated labeling system (Desikan et al., 2006; Fischl et al., 2004). Mean intraclass correlation between this method and manual labeling has been reported to be .84 across all 66 areas, with a mean distance error of less than 1 mm (Desikan et al., 2006). Based on this cortical parcellation, a newly developed algorithm was used to calculate the WM volume in the gyrus underneath each cortical label. Each WM voxel within a gyrus was labeled according to the label of the nearest cortical vertex. Deep WM was not assigned to a particular cortical area, with a 5 mm distance limit. This yielded 33 WM areas in each hemisphere, corresponding to the 33 cortical areas. The volume of each region was obtained by counting the number of 1 mm^3 voxels included (all scans were resampled to 1 mm isotropic voxels during the first FreeSurfer processing step). Estimated ICV was used to correct the volumetric data. WM volume underlying each of the user-defined cortical labels was calculated using similar methods. In particular, each WM voxel within a 5 mm distance of any vertex included in 1 of the cortical labels was classified as part of that specific cortical label's underlying WM volume.

2.4. Visual oddball paradigm and event-related potentials analysis

The 3-stimulus oddball paradigm was modeled on Comerchero and Polich (1999) and Fjell and Walhovd (2004), consisting of standard and target blue ellipses (horizontal and vertical radius = 10.2 and 11 cm for the standard stimuli, and 11.7 and 13.2 cm for the target stimuli). Distractors were large blue squares (28 × 28 cm). The stimuli were thus much larger than those used in Comerchero and Polich (1999) and also somewhat larger than the stimuli employed by Fjell and Walhovd (2004). There were 1000 trials in all with the standard/target/distractor ratio at .80/.10/.10. The stimuli were presented on a 21-inch screen with a uniform black background, at a viewing distance of 100 cm, and visual fields of about 11.7° × 12.6°, 13.4° × 14.3°, and 16° for the standard, target, and distractor stimuli. The stimuli were presented for 500 ms and the interstimulus interval (ISI) was randomly jittered between 0.5 and 2 seconds. The stimuli were presented in a pseudorandom order limited by the rules that all targets were separated by a minimum of 5 standards and that a target never followed directly after a distractor, and vice versa. Participants were

instructed to fixate on the center of the screen and press a button on the response box with their right index finger whenever a target appeared, but never to standards or distractors. The participants were asked to respond as quickly as possible without making mistakes. Thus, both speed and accuracy were emphasized. Before the experimental trials began, participants completed a minimum of 100 practice trials to ascertain their ability to discriminate between standard and target stimuli. Accuracy cutoff criteria were set to 20% for each of the stimulus types, resulting in the exclusion of 1 participant who had 44% omissions.

Continuous EEG was recorded digitally during the task at a sampling rate of 500 points per second with 18 electrodes placed according to the 10–20 system, including frontal (Fz, F7, F3, F8, F4), central (Cz, T3, C3, T4, C4), parietal (Pz, P7, P3, P8, P4), and occipital (Oz, O1, O2) sites. The left mastoid was used as reference, and electrodes placed above and below the left eye and at both canthi were used for eye movement registration. EEG segments of 1-second duration relative to each stimulus presentation were baseline corrected (−200 ms to stimulus onset) and band-pass filtered in the frequency domain of 0.1–20 Hz. Procedures for eye movement correction were used to remove blink artifacts (Semlitsch et al., 1986), and remaining segments containing amplitudes above ± 100 μV were rejected. The modified set of EEG segments were then sorted according to stimulus type and averaged to give the event-related potentials.

Peaks of some ERP components vary substantially between individuals and may be difficult to identify in individual datasets. ERP amplitudes measured as an average in a specified temporal window are less affected by variable latency (Luck, 2005), and may be more stably related to structural measures. We therefore focus on mean amplitude within defined temporal windows in the present study, and peak latency is not reported. Time windows around the ERP components of interest were identified by visual identification based on the grand average plots (i.e., Cz for P3a and Pz for P3b). Mean amplitudes were calculated between 300 and 600 ms for P3a and 400–600 ms for P3b.

2.5. Statistical analysis

First, we asked whether *APOE* genotype was related to ICV, total brain volume, total cortical volume, and total WM volume. Subsequently, to explore the effects of *APOE* polymorphism on regional cortical thickness we conducted a general linear model (GLM) with *APOE* genotype (ε4+, ε4−) as classification variables (main effect). In addition, mean cortical thickness was calculated within labels drawn around the major effect sites to enable visualization and further statistical testing of the cortical thickness and ERP amplitude correlations. We picked out 7 major effect sites and set *p*-value threshold to 0.01, and used this border to mark the areas with labels. A split-half analysis on mean cortical thickness in the labeled areas was performed to explore the stability of the results across samples. To control for false-positives because of multiple comparisons, *p* value distributions for each hemisphere limited by 2 separate α levels ($p \leq 0.05$ and $p \leq 0.01$) were computed to enable inspection of number of vertices with either positive or negative *p* values. The standardized residuals of gyral WM volumes regressed on ICV were submitted to separate univariate analysis of variance (ANOVA) with *APOE* genotype as fixed factor.

ERP amplitudes correlate highly between electrodes, and in a paradigm with central stimulus presentation such as the present, electrodes within each anterior-posterior line (e.g., frontal electrodes) should correlate more strongly than electrodes along the same laterality line (e.g., left side electrodes). To determine which of the electrodes contributed most strongly to the main effect of P3a amplitude, we analyzed the component structure of the P3a amplitudes for 9 electrodes (F3, Fz, F4, C3, Cz, C4, P3, Pz, P4). A principal-component analysis with varimax rotation was used.

To test whether *APOE*-related differences in cortical thickness mediated ERP amplitudes and behavioral stimulus discrimination efficiency, we first calculated Pearson's correlations between cortical thickness in each of the labels with ERP amplitudes, and with target detection accuracy. Subsequently, the information from the ANOVAs and correlation analysis was used in a path analysis based on structural equation modeling to test the hypothesis that effects of *APOE* genotype on behavioral accuracy is mediated by *APOE*-related effects on cortical thickness and ERP amplitude.

The pattern of susceptibility to cognitive decline and dementia may vary with age such that participating ε4 carriers are relatively less susceptible to cognitive decline the older they get (Farrer et al., 1997; Small et al., 2004). Familial risk for dementia (i.e., parents or siblings with diagnosed dementia) may be an index of this effect. We therefore obtained data from 35 of the original 40 subjects on the incidence of first degree relatives with diagnosed dementia. We divided these 35 individuals into 2 age groups (middle-aged and old) and used univariate ANOVAs to check whether *APOE* genotype was associated with reporting parents or siblings with dementia diagnoses. We also used separate univariate ananlysis of covariance (ANCOVA) to test for possible age × genotype interactions. Statistical analyses were done with SPSS 14.0, and the path analysis was done with AMOS 7.0 (SPSS Inc., Chicago, IL).

3. Results

3.1. Intracranial volume, total brain volume, and total cortical and white matter volumes

To test whether the genotype groups differed on global measures of brain structure we performed a series of independent samples *t* tests with *APOE* genotype as grouping variable. Intracranial volume (ICV) did not differ significantly between ε4 carriers and noncarriers [Mean (SD)],

(1,599,366 (155,881) vs. 1,704,687 (323,690) mm^3), [$t_{(38)}$ = 1.31, p = 0.20]. Total brain volumes did not differ significantly between ε4 carriers and noncarriers (1,004,989 (71,188) vs. 1,051,317 (122,958) mm^3), [$t_{(38)}$ = 1.46, p = 0.15]. Next, we tested whether *APOE* genotype modulated total cortical volume and total WM volume. As with ICV and brain volume, cortical and WM volumes did not differ between ε4 carriers and noncarriers (520,046 (38,376) vs. 539,194 (48,814) mm^3 for cortical, [$t_{(38)}$ = 1.38, p = 0.18], and 524,872 (47,892) vs. 554,554 (71,363) mm^3 for WM [$t_{(38)}$ = 1.55, p = 0.13]). When these global measures were corrected for ICV, all trends for lower volumes in ε4 carriers disappeared (p = 0 .50, 0.59, and 0.41 for ICV-corrected brain, cortical, and WM volumes, respectively).

3.2. *APOE*-related regional differences in cortical thickness

A GLM analysis showed several areas where ε4 carriers had significantly thicker cortex than non-carriers (Fig. 2). The largest effect sites were found in the right hemisphere medial orbital frontal gyrus, the right hemisphere parahippocampal gyrus, the right hemisphere sulcus between lateral occipital gyrus and inferior temporal gyrus, the right-sided supramarginal gyrus, right hemisphere sulcus between superior and middle prefrontal gyri, left hemisphere superior prefrontal gyrus, and left hemisphere lateral occipital gyrus. Group differences were unaffected by ICV correction. The only areas estimated to be thicker in noncarriers were 2 small patches on the left inferior temporal gyrus and the left precentral gyrus. As can be seen from Fig. 3, the number of vertices with negative p values is much larger than the number of positive p values for p values lower than 0.05, and especially for p values lower than 0.01. Thus, a large majority of vertices were thicker in ε4 carriers, especially at the more stringent α level (85.4% thicker vertices in left hemisphere, 90.3% in right hemisphere). Labels were drawn around 7 of the largest effect sites (Fig. 4 and Table 2) and mean thickness was calculated in each label for each of the genotype groups.

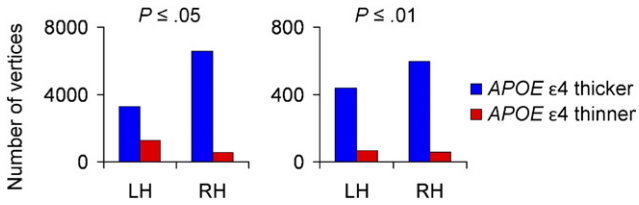

Fig. 3. Number of vertices in left hemisphere (LH) and right hemisphere (RH) significantly thicker (blue) or thinner (red) in *APOE* ε4 carriers. Results for $p \leq 0.05$ (left) and $p \leq 0.01$ (right) are shown.

A split-half strategy was employed to validate the results. The 40 participants were sorted according to *APOE* genotype group (i.e., ε3/ε3, ε3/ε4, ε4/ε4), gender, and age, and then alternately allocated to split-half group 1 or 2. In addition to the factors used in the sorting procedure, IQ and level of education was checked to be similar across sample

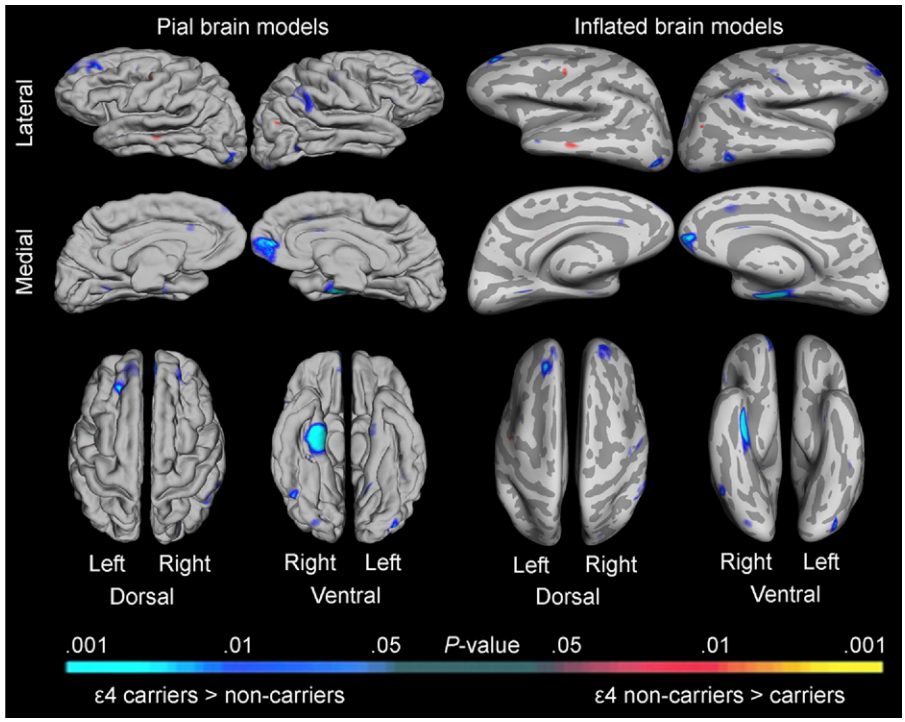

Fig. 2. The pial (left) and inflated (right) brain models show the effect of *APOE* genotype by general linear modeling (different offset, same slope, assumed). Pale gray represents gyri and dark gray represents sulci. Blue and cyan indicate areas where ε4+ participants had significantly thicker cortex than ε4-participants. Red and yellow indicate the inverse relation.

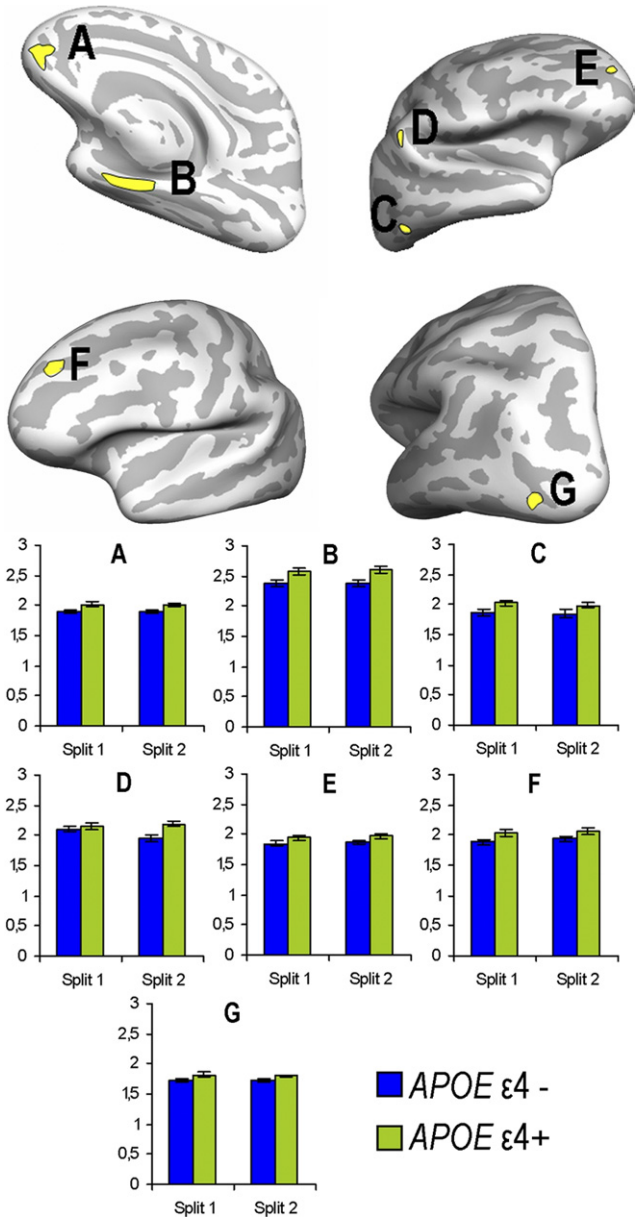

Fig. 4. Inflated brain models showing the extent of the 7 labels chosen on the basis of group differences (as depicted in Fig. 2) and histograms showing mean thickness of each of 7 labels drawn around major areas affected by *APOE* genotype for each split-half group. Cortical thickness in *APOE* ε3 homozygotes is shown in blue and ε4 carriers in green. Effects of *APOE* genotype on cortical thickness were stable as the cortical mantle was thicker in ε4 carriers in both subgroups in all cortical areas. Error bars represent standard error of the mean.

subsets [$t_{(38)}$ = .68, p = 0.50, and $t_{(38)}$ = .05, p = 0.96, respectively]. In Fig. 4, mean thickness of each of the 7 labels was plotted in histograms for both split-half groups. The plots reveal consistency across sample subsets. ε4 carriers had thicker cortex in each of the 7 labels for both sample subsets. This indicates that it is unlikely that the effect of *APOE* ε4 on cortical thickness in the chosen labels is a result of false-positives from multiple statistical comparisons.

Impact of *APOE* genotype on gyral WM volume directly underlying the cortical labels was tested with separate t tests. ICV was regressed out from all the 7 labels based on the areas with cortical thickness difference. There were no significant differences between genotype groups. There was, however, a number of marginal p-values ($0.05 < p < .1$), and WM volumes were in all cases nominally smaller in ε4 carriers, consistent with the global WM volume measure.

3.3. Visual oddball

3.3.1. Behavioral results

Mean accuracy across all subjects and stimulus types was 98.3%, where 1.1%, 7.7%, and 0.7% errors were made on standard, target and distractor stimuli, respectively. There was no difference between *APOE* genotype groups on rate of false alarm responses to standard and distractor stimuli. Target trial miss rate was 5.6% for ε4 noncarriers versus 9.9% for the ε4 carriers [$t_{(38)}$ = 2.04, p = 0.048]. This difference cannot entirely be attributed to different sensitivity because d′ (3.96 and 3.70 for non-ε4 and ε4 respectively) did not reach significance, [$t_{(38)}$ = 1.31, p = 0.199], due to the slightly higher false alarm rate in noncarriers than in carriers (2.0% and 1.7% respectively). Beta and criterion were also nonsignificant. Mean reaction time (RT) to target hits was 511 and 528 ms for ε4 carriers and noncarriers respectively, which was not significantly different [$t_{(38)}$ = .84, p = 0.40].

3.3.2. Amplitudes

To determine which of the electrodes contributed most strongly to the main effect of P3a amplitude, we analyzed the component structure of the P3a amplitudes for 9 electrodes (F3, Fz, F4, C3, Cz, C4, P3, Pz, P4). This resulted in 2 components with total initial eigenvalues of 6.95 and 1.35 respectively, accounting for 77.2% and 15.0% of the total variance. The rotated component matrix (see Supplementary Table 1) indicated that electrodes within each anterior-posterior line constituted relatively unitary groups. We therefore calculated mean amplitudes within each line to yield an estimate of mean frontal (F3, Fz, F4), central (C3, Cz, C4) and parietal (P3, Pz, P4) amplitudes for each participant.

Table 2
List of labels and their approximate brain region

Label	Brain region
A	Right hemisphere medial orbital frontal gyrus.
B	Right hemisphere parahippocampal gyrus.
C	Right hemisphere sulcus between lateral occipital gyrus and inferior temporal gyrus.
D	Right hemisphere supramarginal gyrus in inferior parietal lobule.
E	Right hemisphere sulcus between superior and middle prefrontal gyri.
F	Left hemisphere superior prefrontal gyrus.
G	Left hemisphere lateral occipital gyrus.

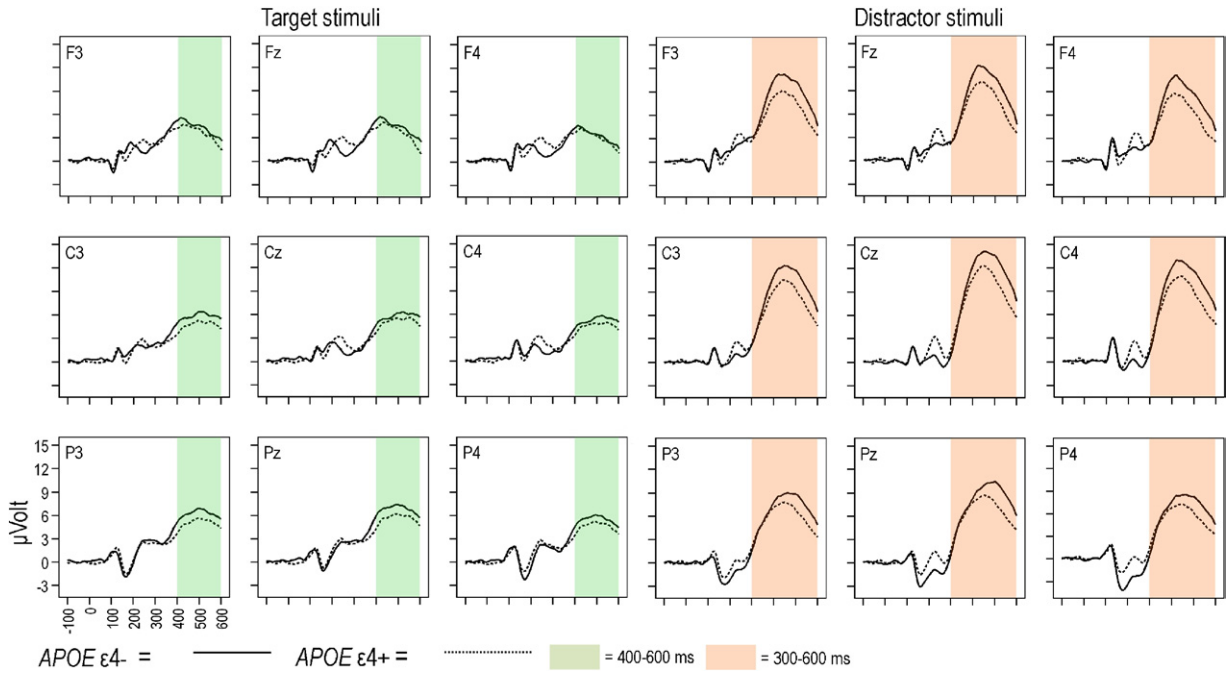

Fig. 5. Visual event-related potentials (ERPs) at frontal, central, and parietal sites. Left, midline, and right electrodes are shown. ERPs to targets are displayed to the left and ERPs to distractors to the right. Transparent colored bars indicate the temporal windows of interest (see bottom of figure for code).

Mean amplitudes (frontal, central, and parietal) were submitted to repeated-measures ANOVA as the within-subjects factor. Genotype group (*APOE* ε4 carrier vs. noncarrier) was set as the between-subject factor. There was a significant main effect of genotype group on mean amplitude, [$F(1,38) = 4.79$, $p = 0.035$] where ε4 carriers had lower amplitudes. There was no interaction between genotype group and within-subjects factors. For target stimuli the same ANOVA strategy as for the distractor trials were used. There were no genotype-related effects, [$F(1,38) = 1.41$, $p = 0.24$]. Grand average ERP curves are presented in Fig. 5.

3.4. Correlations between cortical thickness, event-related potentials amplitudes, and target detection accuracy

Mean thickness in each of the chosen labels were submitted to a series of analyses of correlation with P3a amplitudes. See Table 3 for an overview of correlations. P3a amplitude at frontal electrodes correlated significantly with thickness in label E (right lateral prefrontal lobe). P3a amplitude at central electrodes correlated significantly with mean thickness in label D (right-sided supramarginal gyrus). Parietal P3a amplitude correlated with mean thickness in label F (left lateral prefrontal lobe). All correlations were negative, that is, thicker cortex was associated with lower P3a amplitude. Labels A, B, C, and G were not significantly correlated with P3a amplitudes. There were no significant correlations with P3b amplitudes. Scatter plots of the relation between cortical thickness and P3a amplitudes indicate that the negative correlation may be stronger for the ε4 carrier group (Fig. 6) [r range $-.37$ to $-.29$ for the ε4 carrier group, and $-.19$ to .00 for the ε4 noncarrier group]. However, due to reduced statistical power when the sample is split, no correlation remains significant for 1 genotype group only.

P3a and P3b were highly significantly correlated with each other, [$r = .62$, $r = .60$, and $r = .66$, for Fz, Cz, and Pz, respectively], and with behavioral accuracy. In particular, P3a at frontal electrodes, for which there was both genotype-related differences and significant correlations with cortical thickness, were related to accuracy, [$r = .47$, $p = 0.002$, $r = .40$, $p = 0.01$, $r = .33$, $p = 0.039$, for frontal, central, and parietal electrode amplitudes]. P3b had similar correlations with behavioral accuracy, [$r = .48$, $r = .36$, and $r = .34$ for Fz, Cz, and Pz, respectively]. Cortical thickness did not correlate with target detection accuracy.

Table 3
Pearsons correlations between thickness of cortex in labeled areas and P3a amplitudes

	Labels						
Electrode	A	B	C	D	E	F	G
Frontal	.00	.11	.07	−.26	**−.37***	−.11	−.04
Central	.06	.05	−.06	**−.32***	−.30	−.18	.01
Parietal	.02	.07	−.02	−.27	−.26	**−.33***	.06

* $p < 0.05$, 2-tailed.

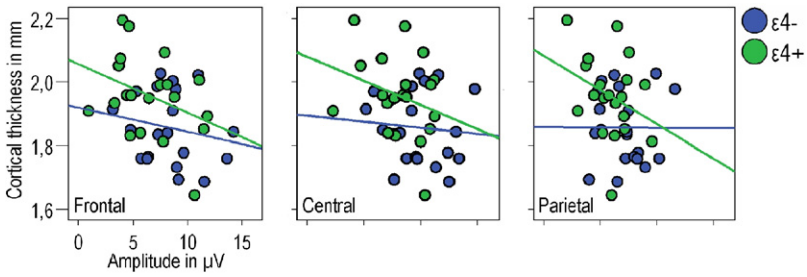

Fig. 6. Scatter plot of relation between cortical thickness of label E (superior-middle prefrontal cortex) and mean amplitude at frontal, central, and parietal electrodes.

3.5. Path analysis

To model causality in the present correlational dataset we made use of a path analysis approach to test the statistical fit of a theoretical model to the data. The model is presented in Fig. 7A. For the present purposes we assume that genotype will modulate brain structure, which in turn may modulate brain physiology and, indirectly, behavioral performance. Based on the results from the ANOVA, correlation analysis, and PCA presented above, this theoretical model was tested in an initial path analysis. Mean thickness in label E (superior-middle prefrontal cortex) was chosen as an index of brain structure, frontal line P3a amplitudes was chosen as an index of brain physiology, and behavioral accuracy represented behavioral performance in the model. As expected, all path estimates were significant, confirming the previous analyses. More importantly, the model yielded a good fit to the data with a relative χ^2 lower than 2 [cmin 3.4/3 df = 1.14] and root mean square error of approximation (rmsea) lower than .05 [rmsea = .021]. According to Browne and Cudeck (1993) a value of the rmsea of about .05 or less would indicate a close fit of the model in relation to the degrees of freedom. In an alternative model genotype modulates each of the phenotypes independently. Only direct paths from genotype to each of the phenotypes were drawn (see Fig. 7B). This model gave a poorer fit to the data. Relative χ^2 was higher than 2 [cmin 11.3/3 df = 3.76], and rmsea higher than .05 [rmsea = .091].

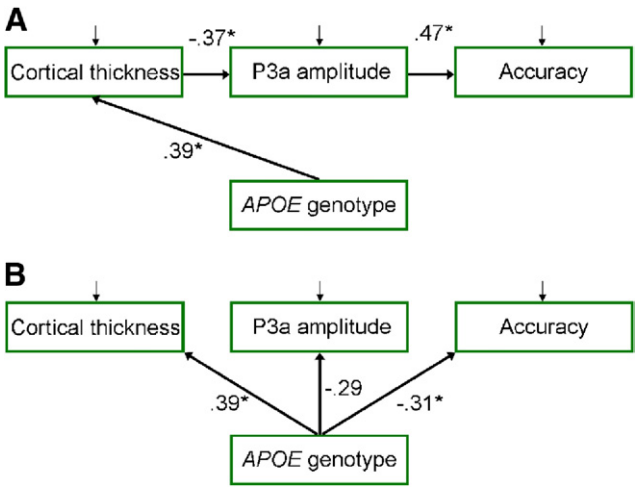

Fig. 7. Path models (A) and (B) of *APOE* genotype, cortical thickness of label E (superior-middle prefrontal cortex), mean P3a amplitude of 3 frontal electrodes (F3, Fz, F4), and target detection accuracy. * Indicate significant paths at level $p < 0.05$. See text for details.

3.6. Influence of familial risk for dementia and participant age

Familial risk for AD was assessed by comparing reported incidence of diagnosed dementia among first degree relatives which was obtained from 35 of the 40 subjects included in the analysis. These were split into 2 age groups (middle-aged (n = 17) and old (n = 18)). The data were submitted to a univariate ANOVA with genotype and age group as fixed factors, and the results showed that there were no significant main effects, but a significant genotype × age group interaction, $F(1,35) = 5.76$, $p = 0.023$. The middle-aged group ε4 was more strongly associated with familial dementia (89%) than ε3 (25%), $t_{(15)} = 3.3$, $p = 0.005$. By contrast, in the old group the pattern was reversed between ε4 carriers (33%) and ε3 homozygotes (44%), although the difference was nonsignificant $t_{(16)} = .46$, $p = 0.65$. Thus, there was a sharp age-related decrease in familial risk for dementia in the ε4 carrier group, but a slight increase in the ε3 homozygote group.

Separate univariate ANOVAs with familial risk for dementia and age group as fixed factors revealed no main effect of familial risk on any of the quantitative MRI, ERP, or behavioral phenotypes used in this study, but there was significant familial risk × age group interaction on the CVLT learning measure (CVLT, 1–5 total), $F(1,35) = 4.44$, $p = 0.043$, and the CVLT delayed recall measure (Long Delay), $F(1,35) = 7.77$, $p = 0.009$. Post hoc analyses with t tests showed that there was no significant difference between middle-aged familial risk groups on delayed recall. However, for the old group participants at increased familial risk had significantly lower delayed recall scores than old participants without increased familial risk ($p = 0.023$).

Separate univariate ANCOVAs with each of the cortical labels as dependent variables, *APOE* genotype as fixed

factor, and age as covariate showed that, with 1 exception, there were no significant or trend-level age × genotype interactions for cortical thickness. The only exception was the left hemisphere lateral occipital gyrus in which ε4 carriers showed an age-related thinning whereas the noncarriers appeared to have a slight thickening of the cortex, [$F(1,39) = 6.36$, $p = 0.016$]. Testing for age × genotype interactions on WM regions of interest (ROIs) with univariate ANCOVAs revealed no significant results. Finally, separate univariate ANCOVAs on each of the ERP components revealed no significant age × genotype interactions.

4. Discussion

The principal focus of interest in the present study was *APOE*-related differences in cortical thickness, and to what extent these differences in cortical thickness mediate attentional function differences between genotype groups. The main results were that: (1) *APOE* genotype modulated regional cortical thickness such that ε4 carriers had thicker cortex than noncarriers in several areas of the cortical mantle; (2) *APOE* genotype modulated ERPs such that ε4 carriers had lower P3a amplitudes than noncarriers, suggesting that *APOE* genotype modulates involuntary aspects of attentional capture possibly related to attentional reorienting processes; (3) regions of the cortical mantle defined by *APOE* genotype differences in thickness correlated significantly with amplitudes on electrodes for which there were also genotype group differences; moreover, these ERP amplitude differences were associated with target detection accuracy, where ε4 carriers scored significantly lower than non-carriers; and (4) path analyses based on structural equation modeling revealed that a model in which behavioral accuracy is mediated by frontal P3a amplitude, which is mediated by frontal cortical thickness, represents a very close fit to the data.

Volumetric measures such as total brain, cortical, and WM volumes have in some studies been shown to be associated with *APOE* genotype (Cohen et al., 2001; Den Heijer et al., 2002; Lemaître et al., 2005; Moffat et al., 2000; Plassman et al., 1997), but these effects are not always found (Adamson et al., 2008; Cherbuin et al., 2008; Reiman et al., 1998; Schmidt et al., 1996). Because volumetric measures are particularly sensitive to ICV variation we opted to check whether the trend level effects on total brain volumes were influenced by regressing out ICV. All trend level effects disappeared with this procedure. Recently, Panizzon et al. (2009) showed in a twin study that cortical surface area and cortical thickness are both highly heritable, but are genetically independent. Because cortical volume is a function of both surface area and thickness, this measure conflates separate underlying genetic factors. Given these lines of evidence it can be argued that regressing ICV out of cortical thickness measures may introduce noise in the data instead of removing it. It is therefore not clear that ICV should be regressed out for these measures. However, if we do, the results are not much altered, consistent with the a priori suggestion.

Regional cortical thickness patterns were very similar to our previous findings (Espeseth et al., 2008), replicating these within a subsample excluding ε2 carriers. Results for all regional labels in the present sample were stable across split-half subsets defined on the basis of genotype, sex, age, IQ, and years of education. *APOE* ε4 was associated with thicker cortex in several areas, many of which are implicated in specified attentional processes and other cognitive processes (Bledowski et al., 2004a; Braver et al., 2001; Corbetta and Shulman, 2002; Corbetta et al., 2008; Kiehl et al., 2001; Linden et al., 1999; Marois et al., 2000; Soltani and Knight, 2000). A processing component specifically related to novelty processing (P3a) was modulated by cortical thickness in a set of areas known to function as nodes in attentional networks. In particular, cortical thickness of the right supramarginal gyrus and an area located between the superior and middle right prefrontal dorsolateral cortex mediated P3a amplitude. Evidence that these areas are involved in generation of P3a, and more generally, attentional reorienting and novelty processing, comes both from human brain lesion studies, functional imaging studies, and from combined morphometric and ERP studies.

Patients with focal prefrontal, temporo-parietal, or posterior medial temporal lobe lesions have attenuated P3a responses to stimuli of auditory, visual, or somatosensory origin (Soltani and Knight, 2000). Furthermore, evidence from patients with prefrontal lesions exposed to deviant stimuli do not show peripheral indexes of attentional orienting such as galvanic skin conductance responses (Knight, 1996) and have also been shown to divert less attention to novel stimuli, which in turn was correlated with an attenuation of the P3a (Daffner et al., 2000). Heterogeneity of lesion localization and extent in clinical groups makes more precise localization of critical cortical areas difficult. Brain imaging studies point to more specific loci within the general regions identified in lesion studies (Bledowski et al., 2004b; Braver et al., 2001; Corbetta and Shulman, 2002; Kiehl et al., 2001; Linden et al., 1999; Marois et al., 2000; Ranganath and Rainer, 2003; Yamaguchi et al., 2004). In a recent meta-analysis on fMRI studies on attentional reorienting Corbetta et al. (2008) showed that the interconnected dorsal and ventral corticocortical networks are typically activated in tasks with infrequent or otherwise unexpected stimuli. According to current thinking, P3a should signal the activation of both networks in addition to regions in the medial temporal lobe and anterior cingulate for rapid attentional reorienting after novel or deviant events (Corbetta et al., 2008; Ranganath and Rainer, 2003; Yamaguchi et al., 2004). These systems seem to be functionally coherent and interconnected even in absence of any specific task. Based on the correlation between regional patterns of spontaneous hemodynamic fluctuations during

rest, Fox et al. (2006) delineated the dorsal and ventral networks and a few regions of overlap. In particular, an area in the middle frontal gyrus, an area near the frontal eye fields, and an area near the temporoparietal junction/supramarginal gyrus, all in the right hemisphere, correlated with both networks. Interestingly, of the areas where cortical thickness was modulated by *APOE* genotype, 3 seem to correspond fairly well to the areas of overlap between the dorsal and ventral networks as delineated by Fox et al. (2006), 2 of which (i.e., labels D and E) also correlate with P3a amplitude (see Fig. 2 in the present study and Figure 5 in Fox et al. (2006) for comparison). Among several other cortical regions, these were recently described as neural hubs characterized by disproportionately high connectivity and also Aβ deposition (Buckner et al., 2009). Healthy ε4 carriers as well as AD patients may be particularly vulnerable to tasks dependent on simultaneous activation of the stimulus-driven and goal-directed attentional systems (Espeseth et al., 2006; Greenwood et al., 2000, 2005; Oken et al., 1994; Parasuraman et al., 1992). Cortical thickness in label E (right superior-middle prefrontal cortex), which corresponds closely to 1 of the major cortical sites reported to generate P3a (Soltani and Knight, 2000; Yamaguchi et al., 2004), mediated genotype-related P3a differences. This suggests that *APOE* genotype modulates neuronal processing efficiency in 1 of several P3a generators and thereby P3a amplitude and novelty processing. The supramarginal gyrus represents a node in the ventral network subserving novelty processing and is also known to be involved in attentional disengagement (Parasuraman et al., 1992), and in this sample predicted amplitude on more posterior electrodes (C3, Cz, C4) than the prefrontal area (primarily F3, Fz, and F4). Parietal P3a amplitude showed a nonsignificant trend for correlation with labels D and E, but was significantly correlated with thickness in the left hemisphere prefrontal label (label F), in contrast to frontal and central amplitudes. It is known from connectivity studies (e.g., Fox et al., 2006) that left frontal and right inferior parietal regions are functionally connected. Because both regions may constitute parts of the ventral reorienting system, one may reasonably expect that the integrity these regions should be associated with reorienting efficiency. It is, however, currently unclear why the correlation between the left frontal area and P3a amplitude seems relatively specific to parietal sites.

It should be recognized that there is a continuing debate in the field as to the specific processes indexed by P3a and P3b, respectively (see Polich, 2007 for a review). For example, traditionally dominant views have stated that P3b amplitude indexes working memory updating or context updating (Donchin and Coles, 1988), or resource allocation (Polich, 1996), whereas P3a amplitude is thought to reflect involuntary and transient attentional allocation to salient stimuli (Courchesne et al., 1975). The oddball task is computationally complex because it conflates several independent processes, as all behavioral tasks do to some extent. ERPs generated by the general target/distractor/standard distinction includes information from processing on whether a response should be made or not (e.g., categorizing the oddball), selecting a response (e.g., go/no-go) based on current stimulus-response mapping, making the response, and generating signals related to performance monitoring. Several of these processes are common to P3a and P3b and there is thus likely to be considerable functional and structural overlap between the processes indexed by these components. In paradigms in which expectations are based on stimulus frequencies, an unexpected event such as an oddball violates these expectations and "signal-driven reorienting" is therefore mediated by the ventral system, perhaps particularly by the frontal areas (Shulman et al., 2009). Violations of expectations signal that a new behavior or sensory stimulation has occurred. This marks an event boundary which requires that the internal cognitive model is updated (Corbetta et al., 2008; Kurby and Zacks, 2008; Zacks et al., 2007). Current theory suggests that the ventral network is activated by task-relevant stimuli, not simply salient stimuli (Indovina and Macaluso, 2007; Kincade et al., 2005). However, the ventral network is activated by irrelevant objects when they are similar (i.e., share features) to the relevant stimuli (contingent attentional capture [Serences et al., 2005]). For example, if targets and oddballs are both infrequent and share the same color (e.g., blue), then one would expect both stimuli to activate the ventral system.

One may speculate that this is 1 of the reasons for the high correlation between distractor related ERP components (e.g., P3a) and behavioral accuracy on target detection. It is well known that the spatial distribution of P3a and P3b as measured on the scalp overlaps to a substantial degree. It should therefore be expected that brain activation elicited by both types of stimuli should correlate with behavioral response. In principle, if the P3a response were to be more stable (i.e., have less variation) than the P3b response, the correlation between P3a amplitude and accuracy could be even stronger than the correlation between P3b amplitude and accuracy.

Based on our previous results of specific attentional deficits (Espeseth et al., 2006) and regionally thicker cortex (Espeseth et al., 2008) in ε4 carriers, we predicted a negative relation between *APOE*-related differences in cortical thickness and attentional function. We reasoned that if the ε4-related cortical thickening is part of a dysfunctional process associated with the ε4 allele, one should expect a negative correlation between thickness in these areas and attentional function for ε4 carriers and positive or no correlation for ε4 non-carriers. The prediction of negative correlation was confirmed for the attention-related P3a component for which the *APOE*-related difference effect was shown to be mediated by cortical thickness in an area thought to be part of a P3a generator network. There was not sufficient statistical power to unambiguously address the prediction of differential thickness P3a amplitude correla-

tion between genotype groups, but the scatter plots in Fig. 6 indicate that the negative relation may be stronger for ε4 carriers.

The small but growing literature on cortical thickness and cognitive function in healthy adults indicate that cortical thickness may be positively correlated with cognitive function (Dickerson et al., 2008; Fjell et al., 2006, 2007; Makris et al., 2007; Walhovd et al., 2006). However, in developing populations the correlation is often negative − thinner cortex has been shown to be associated with better cognitive performance (Shaw et al., 2006; Sowell et al., 2004, 2008). A negative correlation is expected in these populations likely because more mature cortical gray matter (after about age 7.5 years, [Shaw et al., 2007a]) contains fewer synapses and is more myelinated than less mature cortical gray matter (Huttenlocher, 1979; Yakovlev and Lecours, 1967). However, the gray matter/WM boundary is not clear-cut, even in histological analysis (Annese et al., 2004). Thus, in MRI images, unmylinated axonal fibers close to the gray/white boundary may appear to be gray matter tissue, and the gray matter may therefore appear to be thicker. In 1 recent study on children with fetal alcohol spectrum disorders, regions of the cortical mantle was up to 1.2 mm thicker than the average cortical thickness of their healthy age-matched peers, and thickness in these areas were associated with lower verbal and visuo-spatial performance (Sowell et al., 2008). The authors concluded that although prenatal alcohol exposure is generally associated with microcephaly, cortical thickness is sensitive to the regional functional integrity which is in part dependent on regional myelination of axonal fibers.

Interestingly, Shaw et al. (2007b) reported that young ε4 carriers (aged 21 or less) had thinner entorhinal cortices than noncarriers. Cognitive data were unfortunately not reported in this study and it is thus not known whether thinner cortex was associated with better performance as has been shown in other work by the same group. However, in an fMRI study with young ε4 carriers and noncarriers (mean age ~ 22), Mondadori et al. (2007) showed that ε4 was associated with better memory performance and lower blood oxygenation level dependent (BOLD) responses in medial temporal lobe (MTL) regions, a finding interpreted by the authors to indicate enhanced neural efficiency in ε4 carriers. This may be an example of antagonistic pleiotropy in which ε4 have beneficial effects early in life, but negative effects after reproductive age.

Regions of counterintuitively thicker cortex have also been observed in adult samples. Rosas et al. (2002, 2005) reported thicker cortex in Huntington's patients in regions of the cortical surface, and although age-related thinning is generally seen, several studies have reported age-related cortical thickening in specific areas, particularly in medial frontal regions in some samples (Espeseth et al., 2008; Fjell et al., 2009; Salat et al., 2004). Thickness measurements in these areas could be modulated by age-related changes in MR tissue parameters such as T_1 relaxation times, which may be due to age-related demyelination (Davatzikos and Resnick, 2002; Jernigan et al., 2001; Ogg and Steen, 1998). If this hypothesis is correct, regional demyelination could lead to an apparent thickening of the cortical mantle. Another model posits that there is an actual inverse relation between WM volume and thickness of the cortical mantle lying directly above it (Seldon, 2005, 2006). Increased myelination could cause the cortical surface to be stretched tangentially, causing the columnar spacing to increase and the cortical thickness to decrease. The model further suggests that such a thinning of the cortex is associated with better function through increased capacity for differentiating afferent signals. Conceivably, the inverse sequence of events, in which there is a reduction in WM integrity, as has been reported several times for ε4-carriers compared with non-carriers (Bartzokis et al., 2006, 2007; Espeseth et al., 2006; Nierenberg et al., 2005; Persson et al., 2006; Smith et al., 2008), cortical columns would become more tightly packed, making the cortical mantle appear thicker and causing the functional efficiency to drop (Seldon, 2005, 2006; see also Draganski et al., 2006). Thus, both models predict that in MRI images the cortex could be estimated to be thicker because of reduced WM integrity. Although mechanisms like these could in principle explain the current pattern of results, each of the model's predictions would have to be tested in the data set individually. We segmented WM volumes based on the T_1-weighted images in the current sample in an effort to investigate the potential role of WM changes to the present results. However, these volumes are dependent on the same estimation of gray/white boundary as the cortical thickness measures. After controlling for ICV there were only trend-level associations with *APOE*, thus giving limited support to either hypothesis. To investigate this problem further, MRI techniques which can measure group differences in MR tissue parameters more directly would be useful (e.g., T_1 relaxometry, diffusion tensor imaging).

Certainly, other possible *APOE*-related biological mechanisms such as early Aβ aggregation (Reiman et al., 2009) or defective neuronal pruning (Luo and O'Leary, 2005) cannot be excluded. Another account suggests an initial compensatory response to neuronal stress, and progressive age-related loss of compensation (Bondi et al., 2005; Bookheimer et al., 2000). If this account is correct, a longitudinal design in which we followed the participants for another 5–10 years might show that areas where ε4 carriers presently have thicker cortex would even out with time or may end up being thinner in ε4 carriers than noncarriers, in accordance with the results from the cross-sectional data reported in Espeseth et al. (2008). Consistent with the notion that thicker cortex in ε4 carriers may be part of a pathological process are data showing that negative effects of *APOE* ε4 on cognitive and neuropsychological measures are equivalent or larger in samples from middle-aged than

older individuals (Espeseth et al., 2006; Small et al., 2004). The *APOE* ε4 associated risk for AD is also stronger for middle-aged compared with older individuals (Farrer et al., 1997). Thus, the finding of thicker cortex in ε4 carriers may be an indication of underlying pathological processes, or the response to such processes (e.g., compensation), that increases the risk for developing AD later in life. A study including also younger age cohorts, ideally in combination with a longitudinal design, would be informative on this issue.

An additional factor that should be considered is the possibility of differential influence of *APOE* genotype on recruitment over the age span studied. ε4 was more strongly associated with familial risk of dementia for the middle-aged participants but not for old participants. This may indicate that old at risk ε4 carriers did not volunteer for this study, or did not satisfy all inclusion criteria during screening. These sample characteristics may have contributed to the scarceness of evidence for genotype × age interactions, and indicate that at least the old ε4 carriers may not be typical for ε4 carriers in the population. However, this does not explain the finding of better delayed recall for ε4 carriers. ε4 carriers had better delayed recall scores for both age groups. The association between ε4 and episodic memory deficits does not seem to be conclusively established in the literature. Probably due to differences in inclusion/exclusion criteria in healthy samples results vary between studies, with some studies revealing a positive, and some a negative effect of ε4. Consistent with this view, findings from several other studies show positive, or no effect of ε4 (e.g., Jorm et al., 2007; Luciano et al., 2009; Raz et al., 2009; Walhovd et al., 2008). In addition, other studies have shown that *APOE* is a stronger predictor of longitudinal decline in memory performance than cross-sectional differences (Bretsky et al., 2003; Caselli et al., 2004; Mayeux et al., 2001). We speculate that variable selection criteria may influence results in cross sectional studies on episodic memory partly through interactive effects between *APOE* and Aβ.

Because *APOE* is related to elevated risk for AD, we may consider the hypothesis that the findings reflect a pattern of premorbid AD changes. There are 2 major hypotheses on the relation between *APOE* and neurodegeneration (Mahley et al., 2006). In the amyloid hypothesis ε4 is suggested to interact with Aβ to inhibit clearance and/or stimulate deposition of Aβ (Huang et al., 2004), enhance Aβ production (Ye et al., 2005), and increase lysosomal leakage and apoptotic cell death (Ji et al., 2006). In the neuronal repair hypothesis ε4 is thought to lead to deficient neuronal health through enhanced neuron-specific proteolysis where neurotoxic fragments of apolipoprotein E (ApoE) is translocated into the cytosol where they lead to cytoskeletal disruption and mitochondrial dysfunction (Mahley et al., 2006). Thus, according to the neuronal repair hypothesis ApoE may be related to neuronal health throughout the life span, and may therefore have identifiable physiological phenotypes that are distinct from those caused by pathological processes late in life, such as those suggested by the amyloid hypothesis. Notably, our finding of differential effects of *APOE* genotype and familial risk of dementia on brain structure and function may underscore this distinction. *APOE* influenced cortical thickness, ERP amplitudes and target detection accuracy independently from participant age, but interacted with age in the association with familial risk of dementia. In contrast to effects of *APOE*, familial risk was not associated with cortical thickness or ERP amplitudes, but was in interaction with age associated with decreased delayed recall scores, a known hallmark of incipient dementia. These findings seem consistent with the notion that *APOE* can influence brain integrity and function throughout adult life by way of mechanisms partly distinct from those that are typically associated with prodromal AD. Daffner et al. (2001) showed that AD patients had severely reduced P3a in a novelty oddball task. AD patients also show markedly increased reaction times to targets following spatially invalid cues (Parasuraman et al., 1992). Following the reasoning of Greenwood and Parasuraman (2003), reduced P3a and increased cost of invalid spatial cues for ε4 carriers may therefore be a manifestation of a qualitatively similar, but quantitatively different attentional function or dysfunction in AD patients and healthy ε4 carriers. In prior research on *APOE* genotype effects on cortical thickness where we investigated both main effects of genotype and genotype × age interactions, we suggested that carriers of at least 1 ε4 allele showed evidence for steeper thinning slope of the cortical mantle in areas where age-related thinning has been reported in normal aging. In addition, ε4 carriers showed evidence of age-related thinning in areas associated with aggregation of Aβ and cortical thinning in initial stages of Alzheimer's disease (Espeseth et al., 2008). Several reports on cortical thickness in AD and healthy aging using similar methods have been published, making a comparison of results pertinent (Dickerson et al., 2009; Du et al., 2007; Fjell et al., 2009; Lerch et al., 2005; Salat et al., 2004; Singh et al., 2006; Walhovd et al., 2008). For example, Dickerson et al. (2009) showed in 4 independent samples that AD is associated with cortical thinning in widespread regions, including the medial temporal cortex, inferior temporal gyrus, temporal pole, angular gyrus, superior frontal gyrus, superior parietal lobule, supramarginal gyrus, precuneus, inferior frontal sulcus, and the primary visual cortex. The magnitude of thinning seemed to be associated with symptom severity and was most prominent in temporal pole and entorhinal regions, lateral temporal and temporoparietal areas, and the superior and middle frontal gyri, particularly in the right hemisphere. The pattern of thinning in healthy aging overlaps significantly but seems to be better characterized by a relatively stronger frontal thinning (Fjell et al., 2009; Salat et al., 2004). Thus, although there is clearly overlapping patterns, including some prefrontal morpholog-

ical changes in AD, medial and lateral temporal lobe and posterior cortical areas may be more severely affected. Reiman et al. (1996) found that areas of hypometabolism in healthy ε4 carriers overlapped with hypometabolic areas in AD patients, but in addition included more anterior prefrontal areas less affected in AD. In the present sample, *APOE*-related differences in or near MTL and posterior brain areas, with the exception of the supramarginal gyrus, did not correlate with P3a. The supramarginal gyrus is strongly associated with AD, but also with advanced aging (Fjell et al., 2009; Salat et al., 2004). However, without information on the biological mechanisms underlying cortical thinning in this area for the different groups, it is impossible to know whether ApoE-related changes are due to deficient neuronal health or Aβ-related processes. Thus, reduced P3a amplitude in the current sample could be related to processes that mediate P3a deficits in AD, age-related P3a reductions, or both.

APOE ε4 was associated with thicker cortex in several areas. Generally, the finding of increased cortical thickness especially in the right parahippocampal gyrus, situated close to the medial temporal lobe structures known to be vulnerable to volume reduction in early AD, seems inconsistent with the interpretation of the present findings as indicating very early AD. However, as discussed above, the reason for the estimation of thicker cortex in ε4 carriers may be related to changes in underlying WM. Hypothetically, because many of the areas where ε4 carriers had thicker cortex were situated adjacent to areas where ε4 carriers appeared to have thicker cortex in middle age but also a steeper age-related decline (see Espeseth et al., 2008), the data suggest that early thickening may be tied to subsequent thinning. We cannot exclude the possibility that there is a subgroup of participants with early signs of pathology, but the fact that the morphological findings are robust even in a split-half sample indicates that we are faced with general changes affecting the whole group rather than effects in a subgroup. These effects may be more related to the generally elevated risk for AD development in ε4 carriers than to the AD process itself.

In the present study, we chose regions of significant main effects of *APOE* genotype as regions of interest to investigate possible physiological and behavioral correlates. We therefore did not expect genotype × age interactions in these data and in accordance with this expectation, the effects seemed stable over the relatively constrained age range of the sample. Consistent with this, there were no *APOE* × age interactions on the ERP measures.

4.1. Conclusions

In cognitive neurogenetics, a new field of research conceived as a merger between molecular genetics and cognitive neuroscience (see Parasuraman and Greenwood, 2004), a central ambition is to track effects of genetic variability on multiple phenotypic levels of mechanisms. If successful, this should result in convergence between molecular and behavioral levels of knowledge, and indeed, between molecular and diagnostic classifications. One influential strategy toward this goal is to focus on so-called "endophenotypes" (see Meyer-Lindenberg and Weinberger, 2006 for a review) where a coordinated analysis of candidates from morphological, physiological and behavioral levels is potentially fruitful approach exemplified by the present study. Taken together, these results demonstrate convergence of endophenotypes representing attention-related mechanisms at multiple levels of analysis. *APOE* modulated dependent variables at 3 separate levels (morphology, electrophysiology, and behavior). Moreover, genotype group differences on brain structure predicted genotype group differences on brain function, where ERPs acted as a physiological intermediate phenotype linking morphology and behavior. Regarding the nature of the tendency for thicker cortex in ε4 carriers, the correlation with ERP measures seem to indicate that cortical thickening cannot be explained solely as a compensatory response. Rather, ε4 carriers displayed event-related potential reductions qualitatively similar to, but quantitatively smaller than groups with focal lesions in the areas where ε4 carriers had thicker cortex (Ranganath and Rainer, 2003; Soltani and Knight, 2000; Yago et al., 2004). The ε4-related pattern of novelty P3a also resembled ERP results from patients with mild to moderate AD (Daffner et al., 2001). Thus, 1 hypothesis is that *APOE*-related thicker cortex may functionally represent small precursors of broader processes related to accelerated aging and prodromal dementia. However, these data do not rule out the possibility that compensatory responses were initiated but were insufficient to prevent functional decline. The mechanistic factors that drive these phenotypic differences remain to be revealed, and also how these mechanisms can be modulated by other genetic and environmental forces.

4.2. Limitations

The primary limitation in the present study is the relatively modest sample size which has precluded formal methods of adjusting for multiple comparisons. Although we believe the split-half method makes a strong case for the reliability and stability of the data, the confirmation of this pattern of results with permutations tests or false discovery rate would be preferable. Another limitation is the unimodal imaging strategy. Additional MRI sequences sensitive to other biological properties (e.g., T_1 relaxometry) could potentially increase the interpretability of the current finding of ε4-related thicker cortex.

Disclosure statement

There are no actual or potential conflicts of interest, no financial contracts or other financial interests related to the present work for any of the authors.

All subjects provided informed consent according to the

declaration of Helsinki. The project was approved by the Regional Committee for Research Ethics of Southern Norway and a biobank for storage of personalized data were approved by the Department of Health.

Acknowledgements

This research was supported by Norwegian Research Council Grant 154313/V-50 to Ivar Reinvang. The contribution from Stefan Sütterlin on data acquisition, and Marit Hansen Hallberg and the staff at Department of Medical Biochemistry, Rikshospitalet-Radiumhospitalet Medical Center, Oslo, Norway is gratefully acknowledged. We thank Stephan Frye for help with the chromosome 19 illustration. We also thank Raja Parasuraman and Pamela M. Greenwood for useful comments to an earlier draft version of the manuscript.

References

Adamson M.M., Landy K.M., Duong S., Fox-Bosetti S., Ashford J.W., Murphy G.M., Weiner M., Taylor J.L., 2008. Apolipoprotein E varepsilon4 influences on episodic recall and brain structures in aging pilots. Neurobiol. Aging, in press. doi:10.1016/j.neurobiolaging.2008.07.017.

Annese J., Pitiot A., Dinov I.D., Toga A.W., 2004. A myelo-architectonic method for the structural classification of cortical areas. Neuroimage 21, 15–26.

Babiloni C., Benussi L., Binetti G., Cassetta E., Dal Forno G., Del Percio C., Ferreri F., Ferri R., Frisoni G., Ghidoni R., Miniussi C., Rodriguez G., Romani G.L., Squitti R., Ventriglia M.C., Rossini P.M., 2006. Apolipoprotein E and alpha brain rhythms in mild cognitive impairment: a multicentric electroencephalogram study. Ann. Neurol. 59, 323–334.

Bartzokis G., Lu P.H., Geschwind D.H., Edwards N., Mintz J., Cummings J.L., 2006. Apolipoprotein E genotype and age-related myelin breakdown in healthy individuals: implications for cognitive decline and dementia. Arch. Gen. Psychiatry 63, 63–72.

Bartzokis G., Lu P.H., Geschwind D.H., Tingus K., Huang D., Mendez M.F., Edwards N., Mintz J., 2007. Apolipoprotein E affects both myelin breakdown and cognition: implications for age-related trajectories of decline into dementia. Biol. Psychiatry 62, 1380–1387.

Bledowski C., Prvulovic D., Goebel R., Zanella F.E., Linden D.E., 2004a. Attentional systems in target and distractor processing: a combined ERP and fMRI study. Neuroimage 22, 530–540.

Bledowski C., Prvulovic D., Hoechstetter K., Scherg M., Wibral M., Goebel R., Linden D.E.J., 2004b. Localizing P300 Generators in Visual Target and Distractor Processing: A Combined Event-Related Potential and Functional Magnetic Resonance Imaging Study. J. Neurosci. 24, 9353–9360.

Bondi, M.W., Houston, W.S., Eyler, L.T., Brown, G.G., 2005. fMRI evidence of compensatory mechanisms in older adults at genetic risk for Alzheimer disease. Neurology 64, 501–508.

Bondi M.W., Salmon D.P., Monsch A.U., Galasko D., Butters N., Klauber M.R., 1995. Episodic memory changes are associated with the APOE ε4 allele in nondemented older adults. Neurology 45, 2203–2206.

Bookheimer S.Y., Strojwas M.H., Cohen M.S., Saunders A.M., Pericak-Vance M.A., Mazziotta J.C., Small G.W., 2000. Patterns of brain activation in people at risk for Alzheimer's disease. N. Engl. J. Med. 343, 450–456.

Braver T.S., Barch D.M., Gray J.R., Molfese D.L., Snyder A., 2001. Anterior cingulate cortex and response conflict: effects of frequency, inhibition and errors. Cereb. Cortex 11, 825–836.

Bretsky P., Guralnik J.M., Launer L., Albert M., Seeman T.E., 2003. The role of APOE-epsilon4 in longitudinal cognitive decline: MacArthur studies of successful aging. Neurology 60, 1077–1081.

Browne M.W., Cudeck R., 1993. Alternative ways of assessing model fit, in: Bollen, Long (Eds.), Testing structural equation models. Sage, Newbury Park, CA, pp.136–162.

Buckner R.L., Head D., Parker J., Fotenos A.F., Marcus D., Morris J.C., Snyder A.C., 2004. A unified approach for morphometric and functional data analysis in young, old, and demented adults using automated atlas-based head size normalization: reliability and validation against manual measurement of total intracranial volume. Neuroimage 23, 724–738.

Buckner R.L., Sepulcre J., Talukdar T., Krienen F.M., Liu H., Hedden T., Andrews-Hanna J.R., Sperling R.A., Johnson K.A., 2009. Cortical hubs revealed by intrinsic functional connectivity: mapping, assessment of stability, and relation to Alzheimer's disease. J. Neurosci. 29, 1860–1873.

Bundesen C., Habekost T., Kyllingsbaek S., 2005. A neural theory of visual attention: bridging cognition and neurophysiology. Psychol. Rev. 112, 291–328.

Caselli R.J., Reiman E.M., Osborne D., Hentz J.G., Baxter L.C., Hernandez J.L., Alexander G.G., 2004. Longitudinal changes in cognition and behavior in asymptomatic carriers of the APOE e4 allele. Neurology 62, 1990–1995.

Cherbuin N., Anstey K.J., Sachdev P.S., Maller J.J., Meslin C., Mack H.A., Wen W., Easteal S., 2008. Total and regional gray matter volume is not related to APOE* E4 status in a community sample of middle-aged individuals. J. Gerontol. A Biol. Sci. Med. Sci. 63, 501–504.

Cohen R.M., Small C., Lalonde F., Friz J., Sunderland T., 2001. Effect of apolipoprotein E genotype on hippocampal volume loss in aging healthy women. Neurology 57, 2223–2228.

Corbetta M., Kincade J.M., Ollinger J.M., McAvoy M.P., Shulman G.L., 2000. Voluntary orienting is dissociated from target detection in human posterior parietal cortex. Nat. Neurosci. 3, 292–297.

Corbetta M., Patel G., Shulman G.L., 2008. The reorienting system of the human brain: from environment to theory of mind. Neuron 53, 306–324.

Corbetta M., Shulman G.L., 2002. Control of goal-directed and stimulus-driven attention in the brain. Nat. Rev. Neurosci. 3, 201–215.

Corder E.H., Saunders A.M., Strittmatter W.J., Schmechel D.E., Gaskell P.C., Small G.W., Roses A.D., Haines J.L., Pericak-Vance M.A., 1993. Gene dose of apolipoprotein E type 4 allele and the risk of Alzheimer's disease in late onset families. Science 261, 921–923.

Courchesne E., Hillyard S.A., Galambos R., 1975. Stimulus novelty, task relevance, and the visual evoked potential in man. Electroenceph. Clin. Neurophysiol. 39, 131–143.

Comerchero M.D., Polich J., 1999. P3a and P3b from typical auditory and visual stimuli. Clin. Neurophysiol. 110, 24–30.

Daffner K.R., Mesulam M.M., Scinto L.F., Acar D., Calvo V., Faust R., Chabrerie A., Kennedy B., Holcomb P., 2000. The central role of the prefrontal cortex in directing attention to novel events. Brain 123, 927–939.

Daffner K.R., Rentz D.M., Scinto L.F., Faust R., Budson A.E., Holcomb P.J., 2001. Pathophysiology underlying diminished attention to novel events in patients with early AD. Neurology 56, 1377–1383.

Dale A.M., Sereno M.I., 1993. Improved localization of cortical activity by combining EEG and MEG with MRI cortical surface reconstruction: a linear approach. J. Cogn. Neurosci. 5, 162–176.

Dale A.M., Fischl B., Sereno M.I., 1999. Cortical surface-based analysis I: segmentation and surface reconstruction. Neuroimage 9, 179–194.

Davatzikos C., Resnick S.M., 2002. Degenerative age changes in white matter connectivity visualized in vivo using magnetic resonance imaging. Cereb. Cortex 12, 767–771.

Deary I.J., Whiteman M.C., Pattie A., Starr J.M., Hayward C., Wright A.F., Carothers A., Whalley L.J., 2002. Cognitive change and the APOE epsilon 4 allele. Nature 418, 932.

Delis D.C., Kaplan E., Kramer J.H., 2001. D-Kefs: Examiners Manual. Psychological Corporation, San Antonio, TX.

Delis D.C., Kramer J.H., Kaplan E., Ober B.A., 2000. California Verbal Learning Test, 2nd Ed. Psychological Corporation, San Antonio, TX.

Den Heijer T., Oudkerk M., Launer L.J., van Duijn C.M., Hofman A., Breteler M.M., 2002. Hippocampal, amygdalar, and global brain atrophy in different apolipoprotein E genotypes. Neurology 59, 746–748.

Desikan R.S., Ségonne F., Fischl B., Quinn B.T., Dickerson B.C., Blacker D., Buckner R.L., Dale A.M., Maguire R.P., Hyman B.T., Albert M.S., Killiany R.J., 2006. An automated labeling system for subdividing the human cerebral cortex on MRI scans into gyral based regions of interest. Neuroimage 31, 968–980.

Desimone R., Duncan J., 1995. Neural mechanisms of selective visual attention. Annu. Rev. Neurosci. 18, 193–222.

Dickerson B.C., Bakkour A., Salat D.H., Feczko E., Pacheco J., Greve D.N., Grodstein F., Wright C.I., Blacker D., Rosas H.D., Sperling R.A., Atri A., Growdon J.H., Hyman B.T., Morris J.C., Fischl B., Buckner R.L., 2009. The cortical signature of Alzheimer's disease: regionally specific cortical thinning relates to symptom severity in very mild to mild AD dementia and is detectable in asymptomatic amyloid-positive individuals. Cereb. Cortex 19, 497–510.

Dickerson B.C., Fenstermacher E., Salat D.H., Wolk D.A., Maguire R.P., Desikan R., Pacheco J., Quinn B.T., Van der Kouwe A., Greve D.N., Blacker D., Albert M.S., Killiany R.J., Fischl B., 2008. Detection of cortical thickness correlates of cognitive performance: Reliability across MRI scan sessions, scanners, and field strengths. Neuroimage 39, 10–18.

Donchin E., Coles M.G.H., 1988. Is the P300 component a manifestation of context updating? Behav. Brain Sci. 11, 357–374.

Draganski B., Gaser C., Kempermann G., Kuhn H.G., Winkler J., Büchel C., May A., 2006. Temporal and spatial dynamics of brain structure changes during extensive learning. JNeurosci. 23: 6314–6317.

Driscoll I., McDaniel M.A., Guynn M.J., 2005. Apolipoprotein E and prospective memory in normally aging adults. Neuropsychol. 19: 28–34.

Du A.T., Schuff N., Kramer J.H., Rosen H.J., Gorno-Tempini M.L., Rankin K., Miller B.L., Weiner M.W., 2007. Different regional patterns of cortical thinning in Alzheimer's disease and frontotemporal dementia. Brain 130, 1159–1166.

Espeseth T., Greenwood P.M., Reinvang I., Fjell A.M., Walhovd K.B., Westlye L.T., Wehling E., Lundervold A., Rootwelt H., Parasuraman R., 2006. Interactive effects of APOE and CHRNA4 on attention and white matter volume in healthy middle-aged and older adults. Cogn. Affect. Behav. Neurosci. 6, 31–43.

Espeseth T., Westlye L.T., Fjell A.M., Walhovd K.B., Rootwelt H., Reinvang I., 2008. Accelerated age-related cortical thinning in healthy carriers of apolipoprotein E ε4. Neurobiol. Aging 29, 329–340.

Farrer L.A., Cupples L.A., Haines J.L., Hyman B., Kukull W.A., Mayeux R., Myers R.H., Pericak-Vance M.A., Risch N., van Duijn C.M., 1997. Effects of age, sex, and ethnicity on the association between Apolipoprotein E genotype and Alzheimer disease. A meta-analysis. APOE and Alzheimer Disease Meta Analysis Consortium. J. Am. Med. Assoc. 278, 1349–1356.

Fischl B., Dale A.M., 2000. Measuring the thickness of the human cerebral cortex from magnetic resonance images. Proc. Natl. Acad. Sci. U. S. A. 97, 11050–11055.

Fischl B., van der Kouwe A., Destrieux C., Halgren E., Ségonne F., Salat D.H., Busa E., Seidman L.J., Goldstein J., Kennedy D., Caviness V., Makris N., Rosen B., Dale A.M., 2004. Automatically parcellating the human cerebral cortex. Cereb. Cortex 14, 11–22.

Fischl B., Salat D.H., Busa E., Albert M., Dieterich M., Haselgrove C., van der Kouwe A., Killiany R., Kennedy D., Klaveness S., Montillo A., Makris N., Rosen B., Dale A.M., 2002. Whole brain segmentation: automated labeling of neuroanatomical structures in the human brain. Neuron 33, 341–355.

Fischl B., Sereno M.I., Dale A.M., 1999. Cortical surface-based analysis. II. Inflation, flattening, and a surface -based coordinate system. Neuroimage 9, 195–207.

Fjell A.M., Walhovd K.B., 2004. Lifespan changes in P3a. Psychophysiology 41, 575–583.

Fjell A.M., Walhovd K.B., Reinvang I., Lundervold A., Salat D., Quinn B.T., Fischl B., Dale A.M., 2006. Selective increase of cortical thickness in high-performing elderly − structural indices of optimal cognitive aging. Neuroimage 29, 984–994.

Fjell A.M., Walhovd K.B., Fischl B., Reinvang I., 2007. Cognitive function, P3a/ P3b brain potentials, and cortical thickness in aging. Hum. Brain Map. 11, 1098–1116.

Fjell A.M., Westlye L.T., Amlien I., Espeseth T., Reinvang I., Raz N., Agartz I., Salat D., Greve D., Fischl B., Dale A.M., Walhovd K.B., 2009. High consistency of regional cortical thinning in aging across multiple samples. Cereb. Cortex 19, 2001–2012.

Fox, M.D., Corbetta M., Snyder A.Z., Vincent J.L., Raichle M.E., 2006. Spontaneous neuronal activity distinguishes human dorsal and ventral attention systems. Proc. Natl. Acad. Sci. U. S. A. 103, 10046–10051.

Gerdes L.U., Klausen I.C., Sihm I., Faergeman O., 1992. Apolipoprotein E polymorphism in a Danish population compared to findings in 45 other study populations around the world. Genet. Epidemiol. 9, 155–167.

Goldberg T.E., Weinberger D.R. 2004. Genes and the parsing of cognitive processes. Trends Cogn Sci. 8, 325–335.

Green, J., Levey A.I., 1999. Event-related potential changes in groups at increased risk for Alzheimer disease. Arch. Neurol. 56, 1398–1403.

Greenwood P.M., Lambert C., Sunderland T., Parasuraman R., 2005. Effects of apolipoprotein E genotype on spatial attention, working memory, and their interaction in healthy, middle-aged adults: results From the National Institute of Mental Health's BIOCARD study. Neuropsychology 19, 199–211.

Greenwood P.M., Parasuraman R., 2003. Normal gene variation, cognition, and aging. Behav. Cogn. Neurosci. Rev. 2, 278–306.

Greenwood P.M., Sunderland T., Friz J., Parasuraman R., 2000. Genetics and visual attention: Selective deficits in healthy adult carriers of the E4 allele of the apolipoprotein E gene. Proc. Natl. Acad. Sci. U. S. A. 97, 11661–11666.

Halgren E., Marinkovic K., Chauvel P., 1998. Generators of late cognitive potentials in auditory and visual oddball tasks. Electroenceph. Clin. Neurophysiol. 106, 156–164.

Huang Y., Weisgraber K.H., Mucke L., Mahley R.W., 2004. Apolipoprotein E: diversity of cellular origins, structural and biophysical properties, and effects in Alzheimer's disease. J. Mol. Neurosci. 23, 189–204.

Huttenlocher P.R., 1979. Synaptic density in human frontal cortex − developmental changes and effects of aging. Brain Res. 163, 195–205.

Indovina I., Macaluso E., 2007. Dissociation of stimulus relevance and saliency factors during shifts of visuospatial attention. Cereb. Cortex 17, 1701–1711.

Jernigan T.L., Archibald S.L., Fennema-Notestine C., Gamst A.C., Stout J.C., Bonner J., Hesselink J.R., 2001. Effects of age on tissues and regions of the cerebrum and cerebellum. Neurobiol. Aging 22, 581–594.

Ji Z.-S., Müllendorff K., Cheng I.H., Miranda R.D., Huang Y., Mahley R.W., 2006. Reactivity of apolipoprotein E4 and amyloid beta peptide: lysosomal stability and neurodegeneration. J. Biol. Chem. 281, 2683–2692.

Jorm A.F., Mather K.A., Butterworth P., Anstey K.J., Christensen H., Easteal S., 2007. APOE genotype and cognitive functioning in a large age-stratified population sample. Neuropsychology 21, 1–8.

Kiehl K.A., Laurens K.R., Duty T.L., Forster B.B., Liddle P.F., 2001. Neural sources involved in auditory target detection and novelty processing: an event-related fMRI study. Psychophysiology 38, 133–142.

Kincade J.M., Abrams R.A., Astafiev S.V., Shulman G.L., Corbetta M., 2005. An event-related functional magnetic resonance imaging study of voluntary and stimulus-driven orienting of attention. J. Neurosci. 25, 4593–4604.

Knight R.T., 1984. Decreased response to novel stimuli after prefrontal lesions in man. Electroenceph. Clin. Neurophysiol. 59, 9–20.

Knight R.T., 1996. Contribution of human hippocampal region to novelty detection. Nature 383, 256–259.

Knudsen E.I., 2007. Fundamental components of attention. Annu. Rev. Neurosci. 30, 57–78.

Kuperberg G.R., Broome M.R., McGuire P.K., David A.S., Eddy M., Ozawa F., Goff D., West W.C., Williams S.C., van der Kouwe A.J., Salat D.H., Dale A.M., Fischl B., 2003. Regionally localized thinning of the cerebral cortex in schizophrenia. Arch. Gen. Psychiatry 60, 878–888.

Kurby C.A., Zacks J.M., 2008. Segmentation in the perception and memory of events. Trends Cogn. Sci. 12, 72–79.

Lemaître H., Crivello F., Dufouil C., Grassiot B., Tzourio C., Alperovitch A., Mazoyer B., 2005. No epsilon4 gene dose effect on hippocampal atrophy in a large MRI database of healthy elderly subjects. Neuroimage 24, 1205–1213.

Lerch J.P., Pruessner J.C., Zijdenbos A., Hampel H., Teipel S.J., Evans A.C., 2005. Focal decline of cortical thickness in Alzheimer's disease identified by computational neuroanatomy. Cereb. Cortex 15, 995–1001.

Linden D.E., 2005. The p300: where in the brain is it produced and what does it tell us? Neuroscientist 11, 563–576.

Linden D.E.J., Prvulovic D., Formisano E., Vollinger M., Zanella F.E., Goebel R., Dierks T., 1999. The functional neuroanatomy of target detection: an fMRI study of visual and auditory oddball tasks. Cereb. Cortex 9, 815–823.

Luciano M., Gow A.J., Taylor M.D., Hayward C., Harris S.E., Campbell H., Porteous D.J., Starr J.M., Visscher P.M., Deary I.J., 2009. Apolipoprotein E is not related to memory abilities at 70 years of age. Behav. Genet. 39, 6–14.

Luck S.J., 2005. An Introduction to the Event-Related Potential Technique. MIT Press, Cambridge, MA.

Luo L., O'Leary D.D., 2005. Axon retraction and degeneration in development and disease. Annu. Rev. Neurosci. 28, 127–156.

Macaluso E., Frith C.D., Driver J., 2002. Supramodal effects of covert spatial orienting triggered by visual or tactile events. J. Cogn. Neurosci. 14, 389–401.

Mahley R.W., Weisgraber K.H., Huang Y., 2006. Apolipoprotein E4: a causative factor and therapeutic target in neuropathology, including Alzheimer's disease. Proc. Natl. Acad. Sci. U. S. A. 103, 5644–5651.

Makris N., Biederman J., Valera E.M., Bush G., Kaiser J., Kennedy D.N., Caviness V.S., Faraone S.V., Seidman L.J., 2007. Cortical thinning of the attention and executive function networks in adults with attention-deficit/hyperactivity disorder. Cereb. Cortex 17, 1364–1375.

Marois R., Leung H.C., Gore J.C., 2000. A stimulus-driven approach to object identity and location processing in the human brain. Neuron 25, 717–728.

Mauch D.H., Nägler K., Schumacher S., Göritz C., Müller E.-C., Otto A., Pfrieger F.W., 2001. CNS synaptogenesis promoted by glia-derived cholesterol. Science 294, 1354–1357.

Mayeux R., Small S.A., Tang M., Tycko B., Stern Y., 2001. Memory performance in healthy elderly without Alzheimer's disease: effects of time and apolipoprotein-E. Neurobiol. Aging 22, 683–689.

Mesulam M., Small D.M., Vandenberghe R., Gitelman D.R., Nobre A., 2005. A heteromodal large-scale network for spatial attention, in: Itti L., Rees G., Tsotsos J.K. (Eds.), Neurobiology of Attention. Elsevier Academic, Amsterdam.

Meyer-Lindenberg A., Weinberger D.R., 2006. Intermediate phenotypes and genetic mechanisms of psychiatric disorders. Nat. Rev. Neurosci. 7, 818–827.

Moffat S.D., Szekely C.A., Zonderman A.B., Kabani N.J., Resnick S.M., 2000. Longitudinal change in hippocampal volume as a function of apolipoprotein E genotype. Neurology 55, 134–136.

Mondadori C.R., de Quervain D.J., Buchmann A., Mustovic H., Wollmer M.A., Schmidt C.F., Boesiger P., Hock C., Nitsch R.M., Papassotiropoulos A., Henke K., 2007. Better memory and neural efficiency in young apolipoprotein E epsilon4 carriers. Cereb. Cortex 17, 1934–1947.

Narr K.L., Woods R.P., Thompson P.M., Szeszko P., Robinson D., Dimtcheva T., Gurbani M., Toga A.W., Bilder R.M., 2007. Relationships between IQ and regional cortical gray matter thickness in healthy adults. Cereb. Cortex 17, 2163–2171.

Nickerson D.A., Taylor S.L., Fullerton S.M., Weiss K.M., Clark A.G., Stengard J.H., Salomaa V., Boerwinkle E., Sing C.F., 2000. Sequence diversity and large-scale typing of SNPs in the human apolipoprotein E gene. Genome Res. 10, 1532–1545.

Nierenberg J., Pomara N., Hoptman M.J., Sidtis J.J., Ardekani B.A., Lim K.O., 2005. Abnormal white matter integrity in healthy apolipoprotein E epsilon4 carriers. Neuroreport 16, 1369–1372.

Ogg R.J., Steen R.G., 1998. Age-related changes in brain T1 are correlated with iron concentration. Magn. Reson. Med. 40, 749–753.

Oken B.S., Kishiyama S.S., Kaye J.A., Howieson D.B., 1994. Attention deficit in Alzheimer's disease is not simulated by an anticholinergic/antihistaminergic drug and is distinct from deficits in healthy aging. Neurology 44, 657–662.

Panizzon M.S., Fennema-Notestine C., Eyler L.T., Jernigan T.L., Prom-Wormley E., Neale M., Jacobson K., Lyons M.J., Grant M.D., Franz C.E., Xian H., Tsuang M., Fischl B., Seidman L., Dale A., Kremen W.S., 2009. Distinct genetic influences on cortical surface area and cortical thickness. Cereb. Cortex 19, 2728–2735.

Parasuraman R., Greenwood P.M., 2004. Molecular genetics of visuospatial attention and working memory, in: Posner M.I. (Ed.), Cognitive Neuroscience of Attention. Guilford Publications, New York, pp. 245–259.

Parasuraman R., Greenwood P.M., Haxby J.V., Grady C.L., 1992. Visuospatial attention in dementia of the Alzheimer type. Brain 115, 711–733.

Parasuraman R., Greenwood P.M., Sunderland T., 2002. The apolipoprotein E gene, attention, and brain function. Neuropsychology 16, 254–274.

Persson J., Lind J., Larsson A., Ingvar M., Cruts M., Van Broeckhoven C., Adolfsson R., Nilsson L.G., Nyberg L., 2006. Altered brain white matter integrity in healthy carriers of the APOE epsilon4 allele: a risk for AD? Neurology 66, 1029–1033.

Plassman B.L., Welsh-Bohmer K.A., Bigler E.D., Johnson S.C., Anderson C.V., Helms M.J., Saunders A.M., Breitner J.C., 1997. Apolipoprotein E epsilon 4 allele and hippocampal volume in twins with normal cognition. Neurology 48, 985–989.

Polich J., 1996. Meta-analysis of P300 normative aging studies. Psychophysiology 33, 334–353.

Polich J., 2007. Updating P300: an integrative theory of P3a and P3b. Clin. Neurophysiol. 118, 2128–2148.

Ponomareva N.V., Korovaitseva G.I., Rogaev E.I., 2008. EEG alterations in non-demented individuals related to apolipoprotein E genotype and to risk of Alzheimer disease. Neurobiol. Aging 29, 819–827.

Posner M.I., 1980. Orienting of attention. Q. J. Exp. Psychol. 32, 3–25.

Posner M.I., Petersen S.E., 1990. The attention system of the human brain. Annu. Rev. Neurosci. 13, 25–42.

Raber J., Huang Y., Ashford J.W., 2004. ApoE genotype accounts for the vast majority of AD risk and AD pathology. Neurobiol. Aging 25, 641–650.

Ranganath C., Rainer G., 2003. Neural mechanisms for detecting and remembering novel events. Nat. Rev. Neurosci. 4, 193–202.

Raz N., Rodrigue K.M., Kennedy K.M., Land S., 2009. Genetic and vascular modifiers of age-sensitive cognitive skills: effects of COMT, BDNF, ApoE, and hypertension. Neuropsychology 23, 105–116.

Reiman E.M., Caselli R.J., Yun L.S., Chen K., Bandy D., Minoshima S., Thibodeau S.N., Osborne D., 1996. Preclinical evidence of Alzheimer's disease in persons homozygous for the epsilon 4 allele for apolipoprotein E. N. Engl. J. Med. 334, 752–758.

Reiman E.M., Chen K., Liu X., Bandy D., Yu M., Lee W., Ayutyanont N., Keppler J., Reeder S.A., Langbaum J.B., Alexander G.E., Klunk W.E., Mathis C.A., Price J.C., Aizenstein H.J., DeKosky S.T., Caselli R.J., 2009. Fibrillar amyloid-beta burden in cognitively normal people at 3 levels of genetic risk for Alzheimer's disease. Proc. Natl. Acad. Sci. U. S. A. 106, 6820–6825.

Reiman E.M., Uecker A., Caselli R.J., Lewis S., Bandy D., de Leon M.J., De Santi S., Convit A., Osborne D., Weaver A., Thibodeau S.N., 1998. Hippocampal volumes in cognitively normal persons at genetic risk for Alzheimer's disease. Ann. Neurol. 44, 288–291.

Reinvang I., Espeseth T., Gjerstad L., 2005. Cognitive ERPs are related to ApoE allelic variation in mildly cognitively impaired patients. Neurosci. Lett. 382, 346–351.

Rosas H.D., Hevelone N.D., Zaleta A.K., Greve D.N., Salat D.H., Fischl B., 2005. Regional cortical thinning in preclinical Huntington disease and its relationship to cognition. Neurology 65, 745–747.

Rosas H.D., Liu A.K., Hersch S., Glessner M., Ferrante R.J., Salat D.H., van der Kouwe A., Jenkins B.G., Dale A.M., Fischl B., 2002. Regional and progressive thinning of the cortical ribbon in Huntington's disease. Neurology 58, 695–701.

Rosen V.M., Bergeson J.L., Putnam K., Harwel A., Sunderland T., 2002. Working memory and apolipoprotein E: what's the connection? Neuropsychologia 40, 2226–2233.

Salat D.H., Buckner R.L., Snyder A.Z., Greve D.N., Desikan R.S.R., Busa E., Morris J.C., Dale A.M., Fischl B., 2004. Thinning of the cerebral cortex in aging. Cereb. Cortex 14, 721–730.

Schmidt H., Schmidt R., Fazekas F., Semmler J., Kapeller P., Reinhart B., Kostner G.M., 1996. Apolipoprotein E e4 allele in the normal elderly: neuropsychologic and brain MRI correlates. Clin. Genet. 50, 293–299.

Seldon H.L., 2005. Does brain white matter growth expand the cortex like a balloon? Hypethesis and consquences. Laterality 10, 81–95.

Seldon H.L., 2006. Cortical laminar thickness and column spacing in human temporal and inferior parietal lobes: intra-individual anatomical relations. Laterality 11, 226–250.

Semlitsch H.V., Anderer P., Schuster P., Presslich O., 1986. A solution for reliable and valid reduction of ocular artifacts applied to the P300 ERP. Psychophysiology 23, 695–703.

Serences J.T., Shomstein S., Leber A.B., Golay X., Egeth H.E., Yantis S., 2005. Coordination of voluntary and stimulus-driven attentional control in human cortex. Psychol. Sci. 16, 114–122.

Shaw P., Eckstrand K., Sharp W., Blumenthal J., Lerch J.P., Greenstein D., Clasen L., Evans A., Giedd J., Rapoport J.L., 2007a. Attention-deficit/hyperactivity disorder is characterized by a delay in cortical maturation. Proc. Natl. Acad. Sci. U. S. A. 104, 19649–19654.

Shaw P., Greenstein D., Lerch J., Clasen L., Lenroot R., Gogtay N., Evans A., Rapoport J., Giedd J., 2006. Intellectual ability and cortical development in children and adolescents. Nature 440, 676–679.

Shaw P., Lerch J.P., Pruessner J.C., Taylor K.N., Rose A.B., Greenstein D., Clasen L., Evans A., Rapoport J.L., Giedd J.N., 2007b. Cortical morphology in children and adolescents with different apolipoprotein E gene polymorphisms: an observational study. Lancet Neurol. 6, 494–500.

Shulman G.L., Astafiev S.V., Franke D., Pope D.L., Snyder A.Z., McAvoy M.P., Corbetta M., 2009. Interaction of stimulus-driven reorienting and expectation in ventral and dorsal frontoparietal and basal ganglia-cortical networks. J. Neurosci. 8, 4392–4407.

Siegel M., Donner T.H., Oostenveld R., Fries P., Engel A.K., 2008. Neuronal synchronization along the dorsal visual pathway reflects the focus of spatial attention. Neuron 60, 709–719.

Singh V., Chertkow H., Lerch J.P., Evans A.C., Dorr A.E., Kabani N.J., 2006. Spatial patterns of cortical thinning in mild cognitive impairment and Alzheimer's disease. Brain 129, 2885–2893.

Small B.J., Rosnick C.B., Fratiglioni L., Bäckman L., 2004. Apolipoprotein E and cognitive performance: a meta-analysis. Psychol. Aging 19, 592–600.

Smith C.D., Chebrolu H., Andersen A.H., Powell D.A., Lovell M.A., Xiong S., Gold B.T., 2008. White matter diffusion alterations in normal women at risk of Alzheimer's disease. Neurobiol. Aging, in press. doi:10.1016/j.neurobiolaging.2008.08.006.

Soltani M., Knight R.T., 2000. Neural origins of the P300. Crit. Rev. Neurobiol. 14, 199–224.

Sowell E.R., Mattson S.N., Kan E., Thompson P.M., Riley E.P., Toga A.W., 2008. Abnormal cortical thickness and brain-behavior correlation patterns in individuals with heavy prenatal alcohol exposure. Cereb. Cortex 18, 136–144.

Sowell E.R., Thompson P.M., Leonard C.M., Welcome S.E., Kan E., Toga A.W., 2004. Longitudinal mapping of cortical thickness and brain growth in normal children. J. Neurosci. 24, 8223–8231.

Sundstrom A., Marklund P., Nilsson L.G., Cruts M., Adolfsson R., Van Broeckhoven C., Nyberg L., 2004. APOE influences on neuropsychological function after mild head injury: within-person comparisons. Neurology 62, 1963–1966.

Teter B., Xu P.T., Gilbert J.R., Roses A.D., Galasko D., Cole G.M., 2002. Defective neuronal sprouting by human apolipoprotein E4 is a gain-of-negative function. J. Neurosci. Res. 68, 331–336.

Uhlhaas P.J., Singer W., 2006. Neural synchrony in brain disorders: relevance for cognitive dysfunctions and pathophysiology. Neuron 52, 155–168.

Vossel S., Thiel C.M., Fink G.R., 2006. Cue validity modulates the neural correlates of covert endogenous orienting of attention in parietal and frontal cortex. Neuroimage 32, 1257–1264.

Walhovd K.B., Fjell A.M., Dale A.M., Fischl B., Quinn B.T., Makris N., Salat D., Reinvang I., 2006. Regional cortical thickness matters in recall after months more than minutes. Neuroimage 31, 1343–1351.

Walhovd K.B., Fjell A.M., Dale A.M., McEvoy L.K., Brewer J., Karow D.S., Salmon D.P., Fennema-Notestine C., the Alzheimer's Disease Neuroimaging Initiative, 2008. Multi-modal imaging predicts memory performance in normal aging and cognitive decline. Neurobiol. Aging, in press. doi:10.1016/j.neurobiolaging.2008.08.013.

Wechsler D., 1999. Wechsler Abbreviated Scale of Intelligence. Psychological Corporation, San Antonio, TX.

Wisdom N.M., Callahan J.L., Hawkins K.A. The effects of apolipoprotein E on non-impaired cognitive functioning: A meta-analysis. Neurobiol Aging. doi:10.1016/j.neurobiolaging.2009.02.003.

Womelsdorf T., Fries P., 2007. The role of neuronal synchronization in selective attention. Curr. Opin. Neurobiol. 17, 154–160.

Womelsdorf T., Fries P., Mitra P.P., Desimone R., 2006. Gamma-band synchronization in visual cortex predicts speed of change detection. Nature 439, 733–736.

Yago E., Duarte A., Wong T., Barcelo F., Knight R.T., 2004. Temporal kinetics of prefrontal modulation of the extrastriate cortex during visual attention. Cogn. Affect. Behav. Neurosci. 4, 609–617.

Yamaguchi S., Hale L.A., D'Esposito M., Knight R.T., 2004. Rapid prefrontal-hippocampal habituation to novel events. J. Neurosci. 24, 5356–5363.

Yamaguchi S., Knight R.T., 1991. Anterior and posterior association cortex contributions to the somatosensory P300. J. Neurosci. 11, 2039–2054.

Yakovlev P.I., Lecours A.R., 1967. The myelogenetic cycles of regional maturation of the brain, in: Minkowski A. (Ed.), Regional Development of the Brain in Early Life. Blackwell Scientific, Oxford, pp. 3–70.

Ye S., Huang Y., Mullendorff K., Dong L., Giedt G., Meng E.C., Cohen F.E., Kuntz I.D., Weisgraber K.H., Mahley R.W., 2005. Apolipoprotein (apo) E4 enhances amyloid beta peptide production in cultured neuronal cells: apoE structure as a potential therapeutic target. Proc. Natl. Acad. Sci. U. S. A. 102, 18700–18705.

Zacks J.M., Speer N.K., Swallow K.M., Braver T.S., Reynolds J.R., 2007. Event perception: a mind-brain perspective. Psychol. Bull. 133, 273–293.

Supplementary Table 1
Rotated component matrix

Electrode	Rotated component loadings	
	1	2
F3	0.94	0.25
Fz	0.95	0.27
F4	0.91	0.22
C3	0.75	0.60
Cz	0.70	0.65
C4	0.75	0.59
P3	0.33	0.91
Pz	0.29	0.93
P4	0.21	0.91