ELSEVIER

Neurobiology of Aging 29 (2008) 329–340

NEUROBIOLOGY OF AGING

www.elsevier.com/locate/neuaging

Accelerated age-related cortical thinning in healthy carriers of apolipoprotein E ε4

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

[a] *Department of Psychology, University of Oslo, P.O. Box 1094, Blindern, N-0317 Oslo, Norway*
[b] *Department of Medical Biochemistry, Rikshospitalet-Radiumhospitalet Medical Center, Oslo, Norway*

Received 19 May 2006; received in revised form 24 October 2006; accepted 30 October 2006
Available online 11 December 2006

Abstract

Effects of APOE genotype on age-related slopes of cortical thinning was estimated by measuring the thickness of the cerebral cortex on a point-by-point basis across the cortical mantle in 96 healthy non-demented volunteers aged 48–75 years. Fifty nine were APOE ε4− (no ε4 allele) and 37 were ε4+ (1 or 2 ε4 alleles). The genotype groups had similar age, sex and IQ. Two T_1-weighted MP-RAGE sequences were averaged for each participant to yield images with high signal-to-noise ratio, and quantified using semi-automated analysis tools. ε4 carriers had thicker cortex than non-carriers in several frontal and temporal areas in both hemispheres, but showed a steeper age-related decline in adjacent areas. Upon comparison of the ε4-specific age-related thinning with previously published patterns of thinning in normal aging and Alzheimer's disease (AD), we conclude that APOE ε4 may function to accelerate thinning in areas found to decline in aging (medial prefrontal and pericentral cortex), but also to initiate thinning in areas associated with AD and amyloid-β aggregation (occipitotemporal and basal temporal cortex).

Keywords: Apolipoprotein E; Cortical morphometry; Brain aging; Individual differences; Alzheimer's disease

1. Introduction

Gray and white matter volumes shrink with age (Bartzokis et al., 2003; Resnick et al., 2003) and the efficiency of many perceptual and cognitive functions decline in adult aging (e.g. Dobbs and Rule, 1989; Salthouse, 1996). Despite this general trend, there is considerable individual variation, and although many environmental factors modulate brain aging (Raz et al., 2005) genes also play a major role. Twin studies have shown that genetic factors contribute substantially to normal variation in brain volume (Toga and Thompson, 2005) and that heritability is generally high also in old age, but differs between structures (Pfefferbaum et al., 2001, 2000; Sullivan et al., 2001). Candidate gene allelic association methods have been used to address the issue of specific genes involved in individual variation, and one of the most widely studied genes is the apolipoprotein E gene (APOE). The three APOE alleles, ε2, ε3 and ε4, produce three isoforms of a protein (ApoE) that delivers lipids to neurons in the service of synaptogenesis (Mauch et al., 2001). Inheritance of ε4 is associated with increased risk of AD in a gene dose dependent manner (Corder et al., 1993). In animals, the ε4 allele has been associated with impaired repair mechanisms following lesions (Teter et al., 2002). In humans, the ε4 is associated with reduced brain integrity following many kinds of neural insult (Fazekas et al., 2001; Sundstrom et al., 2004) and ε4 is also associated with reduction in cerebral glucose metabolism (Reiman et al., 1996) and reduced cognitive functioning in healthy middle-aged adults (Flory et al., 2000; Greenwood et al., 2000). It has been suggested that APOE may be primarily characterized as a gene involved in neuronal plasticity and repair, and only secondarily as an AD susceptibility gene (Greenwood and

* Corresponding author. Tel.: +47 22845135; fax: +47 22845096.
E-mail address: thomas.espeseth@psykologi.uio.no (T. Espeseth).

0197-4580/$ – see front matter © 2006 Elsevier Inc. All rights reserved.
doi:10.1016/j.neurobiolaging.2006.10.030

Parasuraman, 2003; Teter et al., 2002). Consistent with this, Reiman et al. (2004) reported an association between APOE ε4 and regional patterns of reduction in cerebral glucose metabolism in healthy volunteers as young as the 20s and 30s.

A growing literature shows that APOE ε4 modulates brain morphology in healthy elderly participants, including hippocampal volume (Cohen et al., 2001; Den Heijer et al., 2002; Lemaître et al., 2005; Moffat et al., 2000; Plassman et al., 1997) and amygdalar volume (Den Heijer et al., 2002). Two studies have also shown that APOE ε4 modulates the *rate* of hippocampal atrophy with increasing age (Cohen et al., 2001; Moffat et al., 2000), and behavioral results have also shown steeper age-related decline in cognitive functions for ε4 carriers (Bretsky et al., 2003; Wilson et al., 2002). Morphological studies have so far emphasized measures of memory-related subcortical structures, presumably because APOE ε4 has been thought of primarily as a susceptibility gene for AD, where memory disorder is a cardinal trait. However, functional MRI studies using memory tasks have also shown effects of APOE variation on cortical activation (Bondi et al., 2005; Bookheimer et al., 2000; Lind et al., 2006), and behavioral studies indicate APOE-associated modulation of several cognitive functions known to be dependent on cortical integrity (Espeseth et al., 2006; Greenwood et al., 2005a; Greenwood et al., 2000; Rosen et al., 2002).

Since APOE has been implied as the major susceptibility gene for late-onset AD (Corder et al., 1993), it is important to understand the effects of this gene on regional thickness of the cerebral cortex in older age cohorts. It is well known that widespread thinning of both primary as well as association cortex occurs from middle age and upwards (Salat et al., 2004). Salat et al. (2004) reported prominent age-related thinning in the prefrontal cortex, including areas close to the primary motor and premotor cortex, and also in the calcarine cortex near the striate cortex. Other regions such as the temporal lobes and areas in or near the anterior cingulate cortex seemed to be relatively spared. In fact, regions of the anterior cingulate and some medial orbitofrontal regions revealed significant age-related thickening. While prefrontal thinning and temporal cortex sparing is consistent with previous reports on age-related volume reduction, thinning of motor, premotor and calcarine cortex, and thickening of anterior cingulate cortex were novel findings (see Raz, 2005 for a review). Thus, strict conclusions regarding the influence of age on these cortical areas cannot be drawn at the present stage. However, since the present study focuses on cortical thickness and also employ the same methodology as Salat et al. (2004), we will compare our results with published reports on cortical thickness rather than cortical volume. There are also widespread morphometric effects associated with AD (Lerch et al., 2005). For example, Lerch et al. (2005) showed that AD patients had significantly thinner cortex in anterior and posterior cingulate cortex, the left dorsolateral prefrontal cortex and most of the temporal lobes. Comparison of the results from Salat et al. (2004) and Lerch et al. (2005) reveal that there is not complete overlap between regional patterns of cortical thinning in aging and AD. This fact suggests that it may be worthwhile to directly compare patterns of APOE ε4-related patterns of cortical thickness with age- or AD-related cortical thinning as reported in the literature. Conceivably, if APOE ε4 has an impact on cortical thickness, it could primarily act by speeding up thickness changes in areas reported to change in normal aging, or alternatively, could modulate cortical thickness in areas associated with AD-related cortical thinning.

As part of a larger study on genetic effects on several cognitive and brain parameters we obtained MRI scans from 96 persons aged 48–75 years and submitted these to morphometric analyses. We made use of a methodology that has been validated with histological (Rosas et al., 2002) and manual measurement (Kuperberg et al., 2003), and has proven capable of showing developmental changes in cortical thickness in aging samples (Salat et al., 2004) and different developmental trajectories over the life span dependent on cognitive abilities (Fjell et al., 2006). Thus, measures of cortical thickness are sensitive to changes in normal aging and may have predictive value on successful aging. Since this study is the first to test the effect of APOE genetic variations of cortical morphometry in an older age-cohort, it is important not to restrict the analyses to predefined areas. Thus, the effect of APOE on cerebral cortical thickness was tested on a point-by-point basis across the entire cortical mantle. The present sample's age range and the methodology were chosen to reveal possible age by genotype interactions on local variation in thickness of the cortical mantle in the life period where early morphological changes are beginning to emerge in the subset of individuals who are at risk for developing AD or other types of dementia. The main questions investigated are whether APOE isoforms differently affect cortical thickness and age-related changes in cortical thickness, and whether such changes are mostly similar to normal age-changes or changes that are found in pathological populations, such as participants suffering from AD.

2. Methods

2.1. Participants and neuropsychological characteristics

Ninety-six persons with ages ranging from 48 to 75 years were included in the study after being interviewed and probed for previous or present substance abuse and neurological or psychiatric diseases known to affect the central nervous system. Any person with a history of treatment for any of the above was excluded from further participation. Persons on adequate medication for hypertension, diabetes type II or hypercholesterolemia were not excluded. Participants were recruited through advertisements in local newspapers and all gave their informed consent to their participation, including blood sample, DNA extraction and genotyping. The project was approved by the Regional Committee for Research Ethics

of Southern Norway, and a biobank was approved by the Department of Health.

Participants were given Vocabulary and Matrices subtests of the Norwegian Version of the Wechsler Abbreviated Scale of Intelligence (WASI) (Wechsler, 1999) to estimate general cognitive ability. All participants had an estimated full scale IQ of 85 or above. Participants also were tested with the California Verbal Learning Test II (CVLT-II) as a measure of memory function (Delis et al., 2000), and a battery of neuropsychological tests (see Spreen and Strauss, 1998 for description of tests). Table 1 summarizes the participants' demographic and neuropsychological characteristics. There were no significant sex, IQ or memory score differences between genotype groups, although there was a non-significant trend for ε4 carriers to obtain *better* delayed recall scores on CVLT-II. The full neuropsychological protocols were examined by a board certified clinical neuropsychologist (coauthor Dr. Ivar Reinvang) experienced with assessments of dementia, and based on this one person was excluded from the study.

2.2. DNA extraction and genotyping

Genotyping was performed by real-time 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), 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). The assay was performed as specified by the supplier, except for scaling down the total assay volume from 20 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 T magnet with a conventional head coil was used. Two 3D magnetization prepared rapid gradient echo (MP-RAGE) T_1-weighted sequences, each 8 min and 46 s, were run for all participants. Each volume consisted of 128 sagittal slices (1.33 mm × 1 mm × 1 mm), with an in-plane voxel size of 1 mm^3 and were acquired with TR = 2730 ms, TE = 3.43 ms, TI = 1000 ms, flip angle = 7° and 256 × 256 matrix. The images were transformed to the DICOM format and transferred to a Linux workstation for volumetric analyses. All morphometric analyses were done within the Freesurfer software package. Head size varies between individuals and introduces noise into morphometric studies. To be able to study regional volumetric differences between different groups of participants with possibly different head sizes, it is common to regress out the effect of intracranial volume (ICV) if ICV varies significantly between groups. ICV includes biological material such as meninges and cerebrospinal fluid in addition to brain tissue. To exclude the possibility that genotype-related differences in brain tissue measures could be explained by differences in cranial volumes, we computed ICV using the procedure specified in Buckner et al. (2004). Briefly, the process of atlas normalization equates head size between participants in the study and a pre-specified reference group. The process of automated atlas transformation generates the Atlas scaling factor (ASF) defined as the volume-scaling factor required to match each individual brain to the atlas target. Buckner et al. (2004) showed that the ASF is proportional to ICV for young, old and demented participants. Total brain volume was estimated using the procedures described in 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. The procedures for automatic volumetric measurement of the cortical mantle are described in Salat et al. (2004).

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*-value*
	APOE ε4+			APOE ε4−			
	n	*M*	S.D.	*n*	*M*	S.D.	
Participants (*n* = 96)	37			59			
Male/female	10/27			17/42			.85
Age		63.9	7.9		64.9	7.7	.56
Education		13.6	2.7		14.1	3.0	.40
WASI		120.5	12.6		117.9	11.0	.29
Stroop CW		60.4	17.8		58.1	12.2	.45
TMT A		36.8	11.5		36.2	12.1	.82
TMT B		79.8	28.8		83.2	28.2	.57
Digit-symbol		49.6	12.0		49.8	10.9	.92
CVLT 1–5 total		54.5	13.5		51.3	9.2	.17
CVLT long delay		13.0	3.0		11.9	2.6	.06

Note: Stroop CW, stroop color-word conflict; TMT A and B, trail making test part A and B; digit-symbol from WAIS – R; CVLT 1–5 total, total score on trial 1–5; CVLT long delay, score on 30 min delay recall.

* *P*-values are two-tailed and based on independent samples *t*-tests with APOE genotype as grouping variable.

Cortical thickness measurements were obtained by reconstructing representations of the gray/white matter 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. This method uses both intensity and continuity information from the entire 3D 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 can be 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 non-rigid 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.

2.4. Data analyses

Fifty-nine participants without the ε4 allele were classified as ε4− (1 with ε2/ε2, 16 with ε2/ε3 and 42 with ε3/ε3) and 37 participants with one or two ε4 alleles were classified as ε4+ (7 with ε2/ε4, 22 with ε3/ε4 and 8 with ε4/ε4). For each hemisphere, estimation of statistical effects was generated by computing a general linear model of the effects of APOE genotype and/or age on cortical thickness at each vertex controlling for effects of gender. Two types of designs were used in these analyses. A different offset, same slope (DOSS) design was used to test whether a main effect of group on thickness could be found. A different offset, different slope design was used to test whether cortical thickness was more strongly related to age in one genotype group than in the other. This is conceptually similar to an interaction between age and genotype. In addition, mean cortical thickness was calculated within labels drawn around the major affected areas to enable visualization and further statistical testing of the age by genotype interactions. First we asked whether APOE genotype was related to regionally unspecific measures such as ICV, total brain volume, total cortical volume and total white matter volume. Subsequently, to explore the effects of APOE polymorphism on regional cortical thickness independent of participant age, we conducted a GLM with APOE genotype (ε4+, ε4−) as classification variable assuming identical age-related slopes between groups (main effect). To test whether APOE genotype was associated with different age-related slopes we submitted the data to another GLM where different age-related slopes were allowed to emerge (interaction effect).

Instead of using a corrected *P*-value threshold, scales with the actual *P* values are displayed in the figures. The number of participants in each group is limited and thus, a harsh criterion for multiple comparisons may be too conservative. However, split-half analyses on mean cortical thickness in two affected areas were performed, making it possible to explore the stability of the results across samples.

3. Results

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

To test whether total intracranial volume (ICV) differed between genotype groups we submitted ICV data to an independent samples *t*-test with APOE genotype as grouping variable (ε4+ = 1 or 2 ε4 alleles, $n = 37$, ε4− = 0 ε4 alleles, $n = 59$). The ICV estimation procedures failed for two cases, one from each genotype group. ε4 carriers had smaller ICV than non-carriers (1,591,194 mm^3 versus 1,609,905 mm^3), but this difference was not significant [$t(92) = .57$, $P = .57$]. ICV was therefore not included in subsequent statistical models on cortical thickness.

To test whether APOE genotype was associated with total brain volume or age-related brain volume changes, we submitted the data to a univariate analysis of variance (ANOVA) with total brain volume as dependent variable, APOE genotype as fixed factor and age as covariate. There was no significant difference in total brain volume between genotype groups [$F(1, 96) = 1.14$, $P = .29$] and no difference in age-related volume shrinkage [$F(1, 96) = .76$, $P = .39$] between genotype groups. There was, however, a main effect of age [$F(1, 96) = 8.12$, $P = .005$], indicating that brain volume shrinks with ascending age.

Next, we asked whether APOE modulates total cortical volume or age-related change of total cortical volume. We submitted cortical volume data to a univariate ANOVA with APOE genotype as fixed factor and age as covariate. There was no main effect of APOE genotype [$F(1, 96) = .71$, $P = .4$] or age[$F(1, 96) = .97$, $P = .33$], and no interaction between these variables[$F(1, 96) = .49$, $P = .49$]. Thus, overall cortical volume was stable across genotypes and over the age span included in the present study.

Finally, we tested the genetic and age-related modulation of total white matter volume. A univariate ANOVA with APOE genotype as fixed factor, age as covariate and total white matter volume as dependent variable showed that there was no difference between APOE genotype groups on white matter volume [$F(1, 96) = .85$, $P = .36$], and no difference in age-related trends between genotype groups [$F(1, 96) = .55$, $P = .46$]. There was however a significant main effect of age

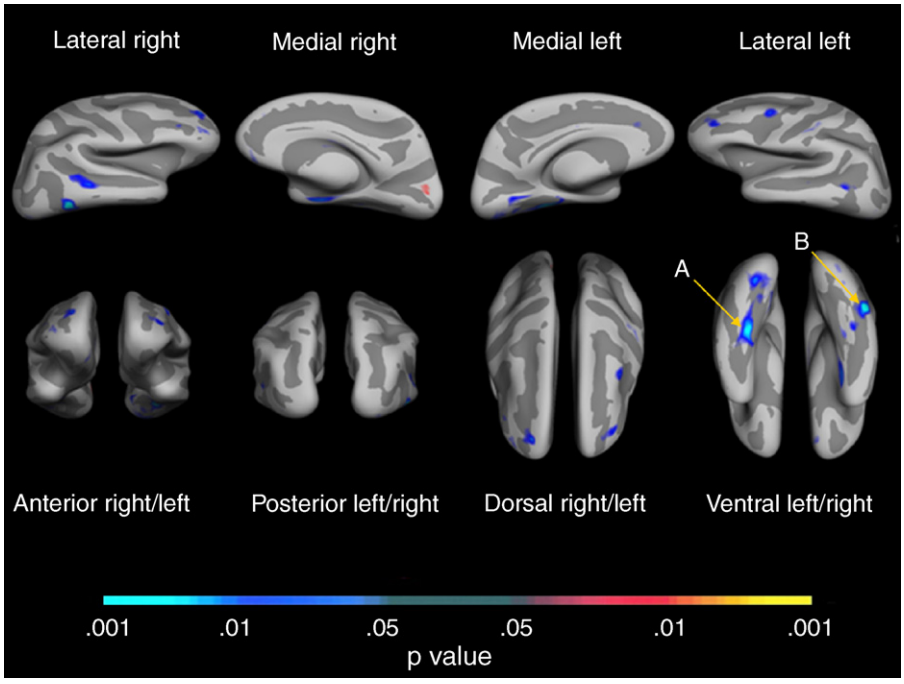

Fig. 1. The inflated brain models show the effect of APOE genotype (across the entire age range), compared by general linear modeling (different onset, same slope, assumed). Pale gray represents gyri and dark gray represents sulci. Blue and cyan indicate areas where ε4+ participants had significantly thicker cortex than ε4− participants. Red and yellow indicates the inverse relation.

[$F(1, 96) = 5.43$, $P = .02$], consistent with the results on total brain volume.

3.2. APOE-related regional differences in cortical thickness

A general linear model (different offsets, same slopes, assumed) controlling for gender and age was computed, and showed several areas where ε4 carriers had significantly thicker cortex than non-carriers (see Fig. 1). Major affected areas were occipital and occipito-temporal areas on both sides, the parahippocampal gyrus on the right side, and several frontal areas in both hemispheres. The only area estimated to be thicker in non-carriers was the right cuneal gyrus. We drew labels around two of the major affected areas (the left occipito-temporal sulcus and an area close to the right anterior occipital sulcus) and calculated mean thickness in both labels for each of the genotype groups (Fig. 2).

3.3. APOE-related modulation of regional aging effects on cortical thickness

In the present work we were primarily interested in how APOE might modulate age-related alterations of cortical thickness. Accordingly, we performed separate GLMs with cortical thickness as the dependent variable and age as the independent variable for each of the genotype groups. As can be seen from Fig. 3a and b both genotype groups displayed a complex patchwork of age-related thinning and thickening. Both groups showed evidence of age-related thinning of the cortex most prominently in occipital areas bilaterally, and bilateral insulas. The ε4+ group seemed to have some additional areas of thinning stretching from the calcarine sulcus towards temporal areas and several patches of thinning around the central sulcus, all effects on both hemispheres. The ε4+ groups also appeared to undergo more pronounced thinning in the insulas but less in the left-sided occipital pole. For both groups there were several areas of age-related thickening, most prominently in frontal areas around gyrus rectus, stretching towards the anterior cinguli on both sides. The age-related thickening appeared to be stronger both in terms of magnitude and spatial extent in the ε4− group.

To estimate areas where age-related thickness trajectories were significantly modulated by APOE genotype we

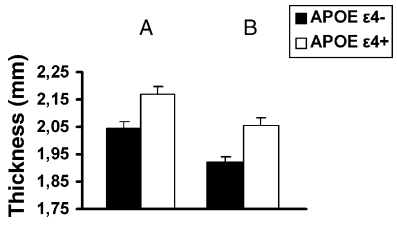

Fig. 2. Mean cortical thickness for APOE genotype groups across age with ε4− thickness represented in black and ε4+ in white. (A) Left hemisphere occipito-temporal area marked with an A in Fig. 1. (B) Right hemisphere occipito-temporal area marked with a B in Fig. 1.

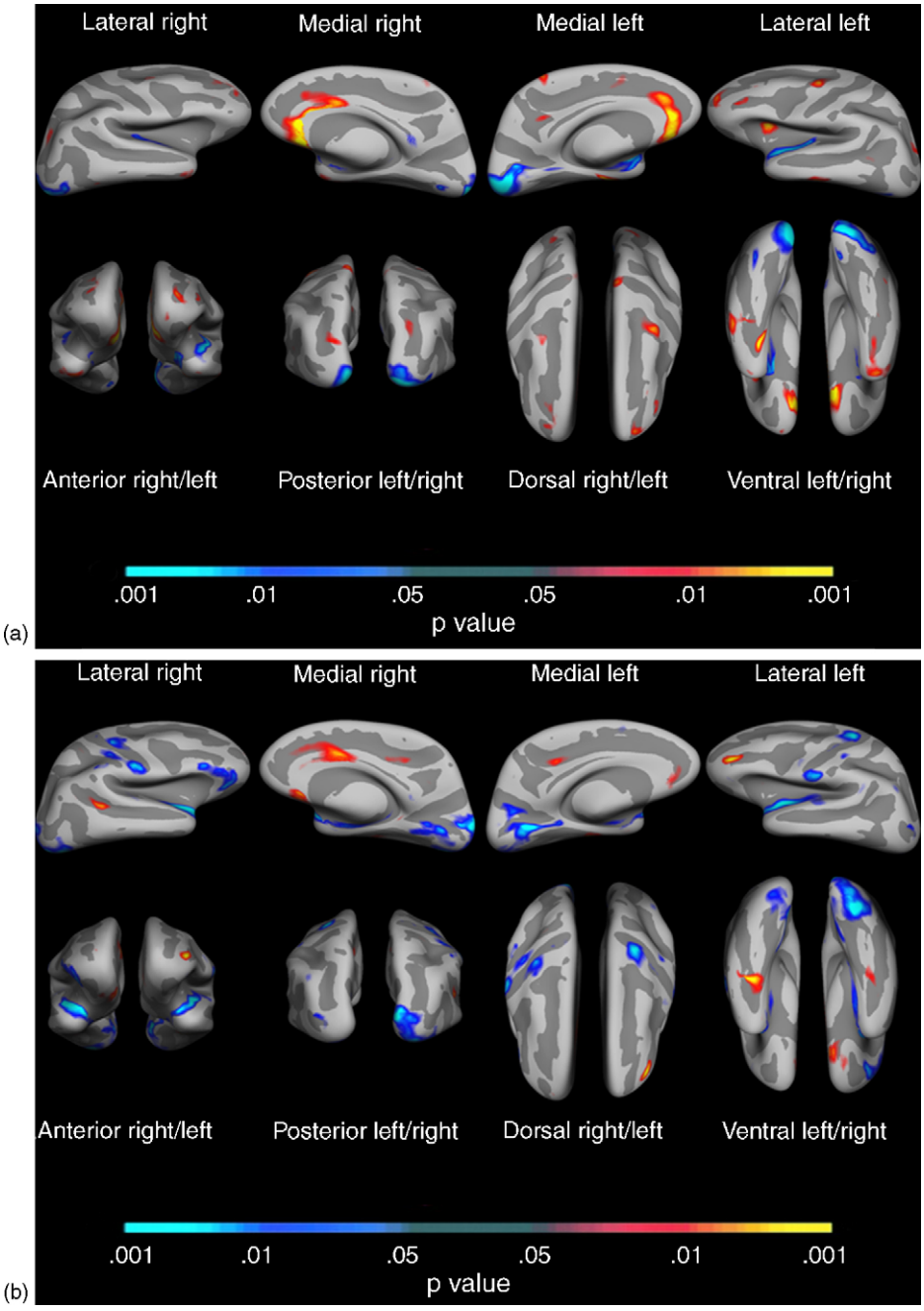

Fig. 3. (a) Age-related cortical thickness development in participants not possessing any ε4 alleles. Blue and cyan indicate age-related thinning whereas red and yellow indicate age-related thickening. (b) Age-related cortical thickness development in carriers of one or two ε4 alleles. Blue and cyan indicate age-related thinning whereas red and yellow indicate age-related thickening.

preformed a separate GLM to test whether the relationship between cortical thickness and age was different between the genotype groups (age × genotype interactions). Results showed that APOE genotype was associated with different age-related developments in several cortical areas as indicated by Fig. 4. A range of affected areas appeared, without exception showing areas, according to genotype by age plots on cortical thickness, where ε4 carriers tended to have thicker cortex in middle-age, but a steeper age-related thinning. Effects were distributed over large areas of the cortical mantle. Most notably, posterior areas such as the right lingual gyrus/fusiform gyrus and several areas on the occipito-parietal border bilaterally showed different age slopes for the two groups. Also, as indicated by the aging results above, several areas along the pre- and postcentral gyri, and the paracentral sulcus showed bilateral evidence for steeper age-related decline in ε4 carriers. Another major effect was found in the left superior

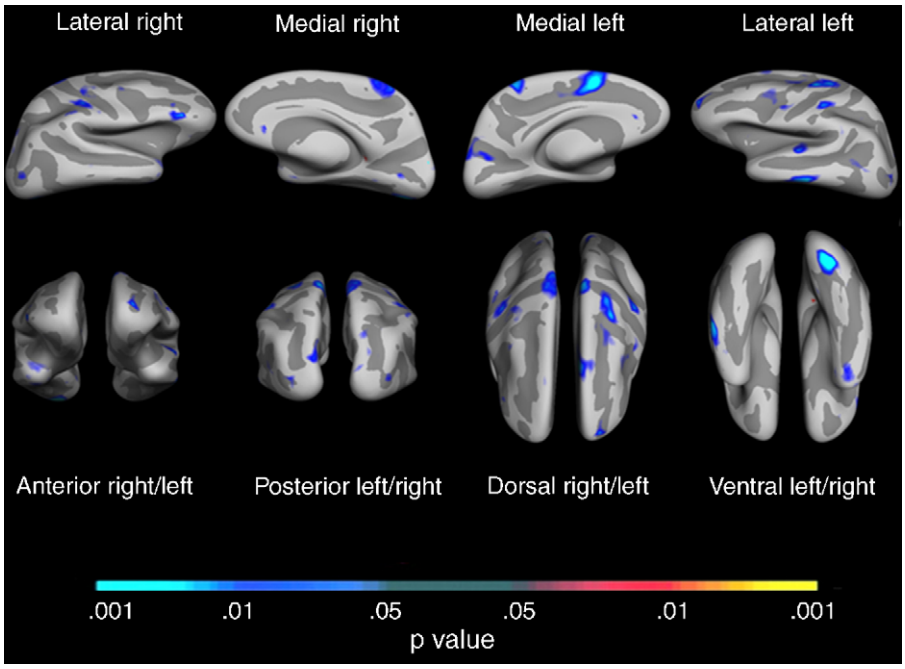

Fig. 4. The inflated brain models show areas with significant APOE genotype x age interaction according to general linear modeling (different onset, different slopes, assumed). Blue and cyan represent areas where ε4+ participants had significantly greater age-related thinning than ε4− participants. Red and yellow indicates the inverse relation.

frontal gyrus, extending ventrally to the supracingular sulcus, in addition to both frontal and temporal areas in both hemispheres.

Multiple comparison correction procedures such as random field theory may be too conservative on the present study due to relatively small sample size, between-subjects analyses, inter-individual variability and small expected effect size. We therefore employed a split-half strategy to validate the results. Based on the GLM results we drew labels around the two major affected areas mentioned above (i.e. the right lingual/fusiform gyrus [Label 1], and the left superior frontal gyrus/supracingular gyrus [Label 2], as outlined in Fig. 5) for which mean cortical thickness was calculated. The 96 participants were sorted according to APOE genotype group, gender, age and IQ, and then the first on the list was allotted to split-half group one, number 2 on the list to split-half group two and so on. In Fig. 5, scatter plots from the two labels are shown for the whole group and for each split-half group. For both labels and both subsets of the sample, ε4 carriers showed a trend towards age-related thinning whereas non-carriers showed a thickening or a relative stability. Confirming the voxel-based GLM, a univariate ANOVA performed on the whole sample with Label 1 as dependent variable, genotype group as fixed factor and age as covariate showed a significant genotype by age interaction on mean cortical thickness in Label 1 [$F(1, 96) = 12.1$, $P = .001$]. The ε4− group showed a trend towards age-related stability [$r = .11$, $P = .39$], whereas the ε4 carriers showed an age-related cortical thinning [$r = -.48$, $P = .003$]. The same tests with Label 2 as dependent variable showed a significant genotype by age interaction [$F(1, 96) = 6.6$, $P = .01$], but here, the ε4 non-carriers age-related slopes were significantly increasing [$r = .34$, $P = .008$], whereas ε4 carriers age-related slopes showed a non-significant trend towards decreasing [$r = -.30$, $P = .07$]. It is known that APOE ε2 may have a protective effect on the brain (Lippa et al., 1997), and is overrepresented among centenarians (Gerdes et al., 2000). In the present study, we had to include participants who were carriers of at least one ε2 allele in both the ε4+ and ε4− groups due to a relatively restricted sample size, as indicated in the methods section. Although the distribution of ε2 carriers were not very different in the genotype groups (28.8% versus 18.9% in ε4− and ε4+ groups, respectively), it is conceivable that the presence of ε2 alleles in the sample would complicate the detection of specific APOE ε4 effects on cortical morphology. To control for ε2-related modulation of cortical thickness we created a new variable classifying each participant as ε2 carrier (ε2+) or ε2 non-carrier (ε2−). In an ANOVA on mean cortical thickness in Label 1, the presence of ε2 was included as a covariate. The APOE genotype × age interaction was essentially unaltered by the inclusion of the new ε2 allele variable [$F(1, 96) = 11.9$, $P = .001$]. The age-related slope of cortical thickness for each genotype group was also not much altered by including the presence of ε2 in the linear regression model. As reported above the ε4− group showed a trend towards age-related stability [$\beta = .09$, $P = .51$], whereas the ε4 carriers showed an age-related cortical thinning [$\beta = -.48$, $P = .003$]. For Label 2 the results of the ANOVA was not influenced by including ε2 allele presence in the model [$F(1, 96) = 6.4$, $P = .01$], whereas the

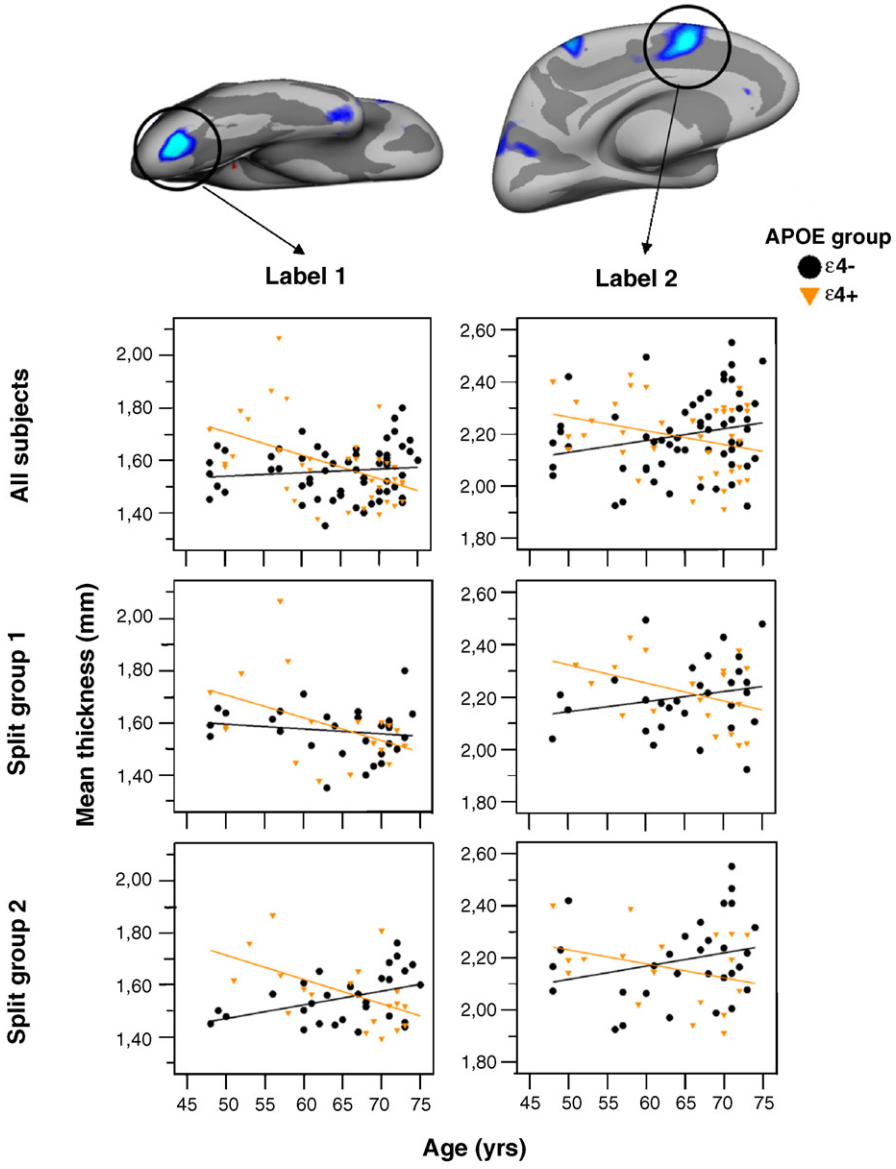

Fig. 5. Scatter plots from the two labels drawn around major effect sites in Fig. 4 (as indicated by arrows). Anatomically, Label 1 encompasses the right lingual/fusiform gyrus, and Label 2 includes the left superior frontal gyrus/supracingular gyrus. The plots show differences in cortical thickness and age-related slopes between ε4+ and ε4− participants. The *Y*-axis shows mean thickness in the chosen labels and the *X*-axis the participant's age. The two scatter plots in the top row show the genotype by age interaction in the chosen labels for all participants. The middle and bottom rows show the same effects for each split half subset of the sample.

significant cortical thickening for the ε4− group disappeared [$\beta = .22$, $P = .09$]. The cortical thinning for the ε4+ group was essentially unaltered [$\beta = -.31$, $P = .07$]. It thus appears that the presence of the ε2 allele may act to accentuate the age-related trend for cortical thickening among ε4 non-carriers, but does not significantly influence the age-related trajectories of ε4 carriers. Since the main focus of the present work is accelerated cortical thinning in ε4 carriers, the presence of the ε2 allele will not be included in subsequent analyses, but see Section 4 for further comments on these results.

ε4 carriers in subsets 1 and 2 showed a trend towards age-related cortical thinning in Label 1 [$r = -.44$, $P = .07$, $r = -.52$, $P = .02$, respectively] and Label 2 [$r = -.31$, $P = .2$, $r = -.40$, $P = .09$, respectively] and according to *t*-tests of Fisher's *z*-transformed correlations, age-related changes were statistically identical for ε4 carriers in subsets 1 and 2 for both labels ($Z < .3$, $P > .05$). In the ε4 non-carrier subsets, the picture was somewhat more mixed in that subsets had different age-related slopes for Label 1 [$Z = 2.21$, $P < .05$, $r = -.16$, $P = .4$, $r = .42$, $P = .02$, for subsets 1 and 2, respectively], but were identical for Label 2 [$Z < .2$, $P > .05$, $r = .26$, $P = .17$, $r = .21$, $P = .27$, for subsets 1 and 2, respectively]. Thus, although the statistical power drops with small groups the general trends in subset one is replicated in subset two.

4. Discussion

The present results reveal for the first time that the APOE gene modulates cortical morphology in healthy middle-aged and older adults. In addition to differences in absolute cortical thickness between genotype groups, APOE significantly modulated aging trajectories by inducing a steeper age-related thinning of several cortical areas for the ε4 carriers.

Total brain and white matter volumes were modulated by age in the present sample, whereas total cortical volume did not vary significantly with age. A number of factors may have contributed to this pattern of results. Raz (2005) pointed out that age-related changes in white and gray matter volumes have different shapes; white matter development show an inverted U-curve, whereas gray matter volume loss seem to be linear or inverted J-shaped. Thus, in samples restricted to participants from middle-age and upwards, significant loss in white matter volume may be revealed together with relative stability of gray matter volumes. The present studies' age range would presumably partly overlap with the tail of a putative inverted J-shaped development of gray matter volume. Thus, the lack of cortical volume effects in the present study could be caused by the constricted age range, not that there were no effects as such. In addition, there may have been little variation in cortical volume because of the relatively stringent screening procedures employed in the present study.

Salat et al. (2004) reported the age-related development of cortical thickness in a normal sample which presumably included both APOE ε4+ and ε4− participants, thus compiling potential genotype-specific effects. We estimated age-related slopes of regional cortical thickness for each genotype group separately. The pattern of age-related thinning and thickening corresponds closely to the results of Salat et al. (2004), although less pronounced, consistent with the present study's smaller age range. Intriguingly, it seems that cortical thinning was more prominent in pericentral, inferior prefrontal, and occipitotemporal areas for ε4 carriers and ε4 non-carriers seemed to have more orbitofrontal and anterior cingulate thickening. Thus, in an interaction model, we directly tested where ε4 carriers had significantly more thinning than ε4 non-carriers.

The present results on APOE genotype are consistent with reports on steeper age-related decline in hippocampal volume (Cohen et al., 2001; Moffat et al., 2000) and cognitive functions such as episodic memory (Bretsky et al., 2003; Wilson et al., 2002) and visuospatial attention (Greenwood et al., 2005b) for carriers of APOE ε4. The participants included in the present study were all thoroughly screened for CNS-related injuries and pathology and had above average cognitive function. Moreover, genotype groups were functionally closely matched, and there were no APOE-related differences on global measures such as ICV, brain volume and total cortical and white matter volumes. APOE-related effects were region-specific, and thus, the effects reported here are not likely to be due to a general physiological or cognitive disadvantage associated with ε4 carriers.

The second major issue was whether ε4 would act by potentiating cortical thinning as observed in normal aging or whether other regions, for example regions typically affected by AD, would be associated with ε4-specific changes. Two major hypotheses on the relation between APOE and neurodegeneration have been proposed (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 the ApoE protein 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. Consistent with this, patterns of cortical thinning in normal aging and AD are only partially overlapping. For example, Lerch et al. (2005) reported severe thinning in the temporal lobes of AD patients compared to age-matched controls, whereas Salat et al. (2004) showed that the temporal lobes are relatively spared in normal aging. Although one should be cautious in the interpretation of comparisons between studies when age ranges vary, it is of interest to see whether the ε4 allele could induce thinning in areas that are relatively spared in non-carriers. Only about 50% of APOE ε4 homozygotes eventually develop AD, suggesting heterogeneous effects of the ε4 allele (Farrer et al., 1997). It is thus likely that a subset of ε4 carriers in the present sample will eventually develop AD while another subset will remain unaffected. Conceivably, each of these subgroups of ε4 carriers will contribute to different patterns of cortical thinning where patterns in one group would resemble age-related thinning and the other AD-related thinning. The ε4+ group as a whole would presumably carry signatures of both age-related and AD-related effects. To explore these issues in the present sample, we compared the pattern of specific APOE ε4-related cortical thinning (as illustrated in Fig. 4) with patterns of thinning reported in AD (Lerch et al., 2005) and with patterns of thinning in a normal aging sample, where all APOE genotypes are likely to be represented (Salat et al., 2004). There is considerable overlap between APOE-affected areas in the present study and affected areas in reports on normal age-related cortical thinning. For example, Salat et al. (2004) reported pronounced thinning in and around the central sulcus, medial prefrontal cortex, parietal cortex, and in occipital areas near the primary visual cortex. Fig. 4 shows that APOE modulated age-related thinning in all these areas, indicating that ε4+ participants may have accelerated thinning in these areas. Interestingly, ε4 carriers seem to have

additional areas of thinning previously reported to be thinner in AD patients compared to age-matched controls (Lerch et al., 2005), specifically in the occipital-temporal area near the lingual and fusiform gyri in the right hemisphere [Label 1 in Fig. 5]. ε4 carriers in the present study had a steeper thinning slope in this area, which is specifically identified by Braak and Braak (1997) as vulnerable to aggregation of Aβ in the initial stage of AD development. Other bilateral temporal lobe areas show the same ε4 allele-specific pattern. Thus, greater age-associated cortical thinning in ε4+ than in ε4− participants may be related to a range of biological processes including Aβ-related pathologies and other progressive deficits not related to Aβ. The present results may indicate that ε4 carriers are subject to both classes of pathological mechanisms attributed to the APOE ε4 isoform by showing accelerated thinning in areas relatively spared in AD, but also in areas where AD patients have thinner cortex than normal controls and also show evidence of Aβ-peptide aggregation.

APOE ε4 was associated with thicker cortex in several areas. Among these areas was the right-sided parahippocampal gyrus, situated close to the medial temporal lobe structures known to be vulnerable to volume reduction in early AD. While one might suspect that the ε4 should be associated with thinner cortex in this area, several factors may have contributed to obscure such a result. Medial temporal lobe volume reduction is not unequivocally associated with APOE ε4. Lemaître et al. (2005) reported hippocampal volume reduction for ε4/ε4 homozygotes compared to non-carriers, but no difference between non-carriers and ε3/ε4 heterozygotes, despite the very large sample size ($n = 1389$). This is consistent with a range of other studies which have attempted to reveal APOE genotype effects on hippocampal volume (Cohen et al., 2001; Moffat et al., 2000; Reiman et al., 1998; Soininen et al., 1995). In addition, ε4 carriers showed a trend towards better delayed free recall scores ($P = .06$), known to depend on hippocampal function (e.g. Scoville and Milner, 1957). 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, suggesting that early thickening may be tied to subsequent thinning. A range of biological mechanisms, including early aggregation of Aβ or defective neuronal pruning (Luo and O'Leary, 2005) in the brains of ε4 carriers, could lead to subsequent neuronal shrinkage and synaptic loss. 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 these participants for another 5–10 years might show that areas where ε4 carriers have thicker cortex now would even out between groups or may be thinner in ε4 carriers than non-carriers, in accordance with the results from the interaction analyses. 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 middle-aged samples than in older samples (Espeseth et al., 2006; Small et al., 2004). The APOE ε4 associated risk for AD is also stronger for middle-aged compared to older samples (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. However, cortical thickness may reflect a number of anatomical and physiological factors and further interpretation needs to take into account functional data.

In conclusion, carriers of at least one ε4 allele show 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 show evidence of age-related thinning in areas associated with aggregation of Aβ and cortical thinning in initial stages of Alzheimer's disease. These findings indicate that APOE genetic variations influence the thickness of the cerebral cortex in specific areas, both by accelerating seemingly normal age-related thinning, and possibly by introducing thinning in areas not normally affected by age. They also indicate that the rate of age-related cortical thinning in general has been overestimated due to failure to differentiate between genotype groups. On the other hand, the post hoc analysis on the influence of APOE ε2 indicate that the ability for compensatory responses may have been underestimated in studies on age-related cortical thinning. Given sufficiently large sample size, genotypes ε2/ε2 and ε2/ε3 should be separated into an ε2 allele group to be compared to an ε3 homozygote group and an ε4 carrier group.

Conflict of interest

No conflicts of interest.

Acknowledgements

Supported by Norwegian Research Council Grant 154313/V50 to Ivar Reinvang. The contribution from Marit Hansen Hallberg and the staff at Department of Medical Biochemistry, Rikshospitalet-Radiumhospitalet Medical Center, Oslo, Norway is gratefully acknowledged.

References

Bartzokis, G., Cummings, J.L., Sultzer, D., Henderson, V.W., Nuechterlein, K.H., Mintz, J., 2003. White matter structural integrity in healthy aging adults and patients with Alzheimer disease: a magnetic resonance imaging study. Arch. Neurol. 60 (3), 393–398.

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 (3), 501–508.

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 (7), 450–456.

Braak, H., Braak, E., 1997. Diagnostic criteria for neuropathologic assessment of Alzheimer's disease. Neurobiol. Aging 18, S85–S88.

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 (7), 1077–1081.

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.

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.

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.

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.

Delis, D.C., Kramer, J.H., Kaplan, E., Ober, B.A., 2000. California Verbal Learning Test, second ed. The 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.

Dobbs, A.R., Rule, B.G., 1989. Adult age differences in working memory. Psychol. Aging 4 (4), 500–503.

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.

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. JAMA 278, 1349–1356.

Fazekas, F., Strasser-Fuchs, S., Kollegger, H., Berger, T., Kristoferitsch, W., Schmidt, H., Schiefermeier, M., Schwarz, C., Kornek, B., Reindl, M., Huber, K., Grass, R., Wimmer, G., Vass, K., Pfeiffer, K.H., Hartung, H.P., Schmidt, R., 2001. Apolipoprotein E epsilon 4 is associated with rapid progression of multiple sclerosis. Neurology 57, 853–857.

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

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.

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 (3), 984–994.

Flory, J.D., Manuck, S.B., Ferrell, R.E., Ryan, C.M., Muldoon, M.F., 2000. Memory performance and the apolipoprotein E polymorphism in a community sample of middle-aged adults. Am. J. Med. Genet. 96 (6), 707–711.

Gerdes, L.U., Jeune, B., Ranberg, K.A., Nybo, H., Vaupel, J.W., 2000. Estimation of apolipoprotein E genotype-specific relative mortality risks from the distribution of genotypes in centenarians and middle-aged men: apolipoprotein E gene is a "frailty gene," not a "longevity gene". Genet. Epidemiol. 19 (3), 202–210.

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

Greenwood, P.M., Lambert, C., Sunderland, T., Parasuraman, R., 2005a. 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 (2), 199–211.

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.

Greenwood, P.M., Sunderland, T., Putnam, K., Levy, J., Parasuraman, R., 2005b. Scaling of visuospatial attention undergoes differential longitudinal change as a function of APOE genotype prior to old age: results from the NIMH BIOCARD study. Neuropsychology 19 (6), 830–840.

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.

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.

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.

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 (4), 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 (7), 995–1001.

Lind, J., Persson, J., Ingvar, M., Larsson, A., Cruts, M., Van Broeckhoven, C., Adolfsson, R., Backman, L., Nilsson, L.G., Petersson, K.M., Nyberg, L., 2006. Reduced functional brain activity response in cognitively intact apolipoprotein E epsilon4 carriers. Brain 129, 1240–1248.

Lippa, C.F., Smith, T.W., Saunders, A.M., Hulette, C., Pulaski-Salo, D., Roses, A.D., 1997. Apolipoprotein E-epsilon 2 and Alzheimer's disease: genotype influences pathologic phenotype. Neurology 48 (2), 515–519.

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

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.

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.

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.

Pfefferbaum, A., Sullivan, E.V., Carmelli, D., 2001. Genetic regulation of regional microstructure of the corpus callosum in late life. Neuroreport 12 (8), 1677–1681.

Pfefferbaum, A., Sullivan, E.V., Swan, G.E., Carmelli, D., 2000. Brain structure in men remains highly heritable in the seventh and eighth decades of life. Neurobiol. Aging 21, 63–74.

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.

Raz, N., 2005. The aging brain observed in vivo: differential changes and their modifiers. In: Cabeza, R., Nyberg, L., Park, D.C. (Eds.), The Cognitive Neuroscience of Aging. Oxford University Press, New York, pp. 19–58.

Raz, N., Lindenberger, U., Rodriue, K.M., Kennedy, K.M., Head, D., Williamson, A., Dahle, C., Gerstorf, D., Acker, J.D., 2005. Regional brain changes in aging healthy adults: general trends, individual differences and modifiers. Cereb. Cortex 15 (11), 1676–1689.

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 (12), 752–758.

Reiman, E.M., Chen, K., Alexander, G.E., Caselli, R.J., Bandy, D., Osborne, D., Saunders, A.M., Hardy, J., 2004. Functional brain abnormalities in young adults at genetic risk for late-onset Alzheimer's dementia. Proc. Natl. Acad. Sci. U.S.A. 101 (1), 284–289.

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 (2), 288–291.

Resnick, S.M., Pham, D.L., Kraut, M.A., Zonderman, A.B., Davatzikos, C., 2003. Longitudinal magnetic resonance imaging studies of older adults: a shrinking brain. J. Neurosci. 23 (8), 3295–3301.

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., Harwell, A., Sunderland, T., 2002. Working memory and apolipoprotein E: what's the connection? Neuropsychologia 40 (13), 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.

Salthouse, T.A., 1996. The processing-speed theory of adult age differences in cognition. Psychol. Rev. 103 (3), 403–428.

Scoville, W.B., Milner, B., 1957. Loss of recent memory after bilateral hippocampal lesions. J. Neurol. Neurosurg. Psychiatry 20, 1–21.

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

Soininen, H., Partanen, K., Pitkanen, A., Hallikainen, M., Hanninen, T., Helisalmi, S., Mannermaa, A., Ryynanen, M., Koivisto, K., Riekkinen Sr., P., 1995. Decreased hippocampal volume asymmetry on MRIs in nondemented elderly subjects carrying the apolipoprotein E epsilon 4 allele. Neurology 45 (2), 391–392.

Spreen, O., Strauss, E., 1998. A Compendium of Neuropsychological Tests: Adminstration, Norms and Commentary, second ed. Oxford University Press, New York.

Sullivan, E.V., Pfefferbaum, A., Swan, G.E., Carmelli, D., 2001. Heritability of hippocampal size in elderly twin men: equivalent influence from genes and environment. Hippocampus 11 (6), 754–762.

Sundstrom, A., Marklund, P., Nilsson, L.G., Cruts, M., Adolfsson, R., Van Broeckhoven, C., Nyberg, L., 2004. Neurology 62 (11), 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.

Toga, A.W., Thompson, P.M., 2005. Genetics of brain structure and intelligence. Annu. Rev. Neurosci. 28, 1–23.

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

Wilson, R.S., Schneider, J.A., Barnes, L.L., Beckett, L.A., Aggarwal, N.T., Cochran, E.J., Berry-Kravis, E., Bach, J., Fox, J.H., Evans, D.A., Bennett, D.A., 2002. The apolipoprotein E epsilon 4 allele and decline in different cognitive systems during a 6-year period. Arch. Neurol. 59, 1154–1160.

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.