Published in final edited form as:
Neuroimage. 2009 May 1; 45(4): 1090–1098. doi:10.1016/j.neuroimage.2009.01.009.

Mapping the effect of *APOE* ε4 on gray matter loss in Alzheimer's disease *in vivo*

M Pievani[1,2], **PE Rasser**[3,4], **S Galluzzi**[1], **L Benussi**[5], **R Ghidoni**[5], **F Sabattoli**[1], **M Bonetti**[6], **G Binetti**[5], **PM Thompson**[7], and **GB Frisoni**[1,8,9]

[1]LENITEM Laboratory of Epidemiology, Neuroimaging and Telemedicine, IRCCS Centro San Giovanni di Dio -FBF, Brescia, Italy

[2]Neuroimaging Research Unit, Department of Neurology, Scientific Institute and University Ospedale San Raffaele, Milan, Italy

[3]Schizophrenia Research Institute, Sydney, Australia

[4]Priority Centre for Brain & Mental Health Research and School of Design, Communication & I.T., University of Newcastle, Newcastle, Australia

[5]Laboratory of Neurobiology, IRCCS Centro San Giovanni di Dio - FBF, Brescia, Italy

[6]Service of Neuroradiology, Istituto Clinico Citta' di Brescia, Brescia, Italy

[7]Laboratory of Neuroimaging, Department of Neurology, UCLA School of Medicine, Los Angeles, CA, USA

[8]Psychogeriatric Ward, IRCCS Centro San Giovanni di Dio FBF

[9]A.Fa.R. Associazione Fatebenefratelli per la Ricerca, Roma, Italy

Abstract

Previous studies suggest that in Alzheimer's disease (AD) the Apolipoprotein E (*APOE*) ε4 allele is associated with greater vulnerability of medial temporal lobe structures. However, less is known about its effect on the whole cortical mantle. Here we aimed to identify *APOE*-related patterns of cortical atrophy in AD using an advanced computational anatomy technique. We studied 15 AD patients carriers (ε4+, age:72±10SD years, MMSE:20±3SD) and 14 non-carriers (ε4-, age:69±9, MMSE:20±5) of the ε4 allele and compared them to 29 age-and-sex matched controls (age:70±9, MMSE:28±1). Each subject underwent a clinical evaluation, a neuropsychological battery, and high-resolution MRI. UCLA's cortical pattern matching technique was used to identify regions of local cortical atrophy. ε4+ and ε4- patients showed similar performance on neuropsychological tests ($p>.05$, *t*-test). Diffuse cortical atrophy was detected for both ε4+ ($p=.0001$, *permutation test*) and ε4- patients ($p=.0001$, *permutation test*) relative to controls, and overall gray matter loss was about 15% in each patients group. Differences in gray matter loss between carriers and non-carriers mapped to the temporal cortex and right occipital pole (20% greater loss in carriers) and to the posterior cingulate, left orbitofrontal and dorsal fronto-parietal cortex (5-15% greater loss in non-carriers). *APOE* effect in AD was not significant ($p>.74$, ANOVA), but a significant *APOE* by region (temporal

Correspondence to: Giovanni B. Frisoni, MD, Laboratory of Epidemiology, Neuroimaging and Telemedicine, IRCCS Centro San Giovanni di Dio - FBF, The National Centre for Research and Care of Alzheimer's and Mental Diseases, via Pilastroni 4, 25125 Brescia, Italy. Tel: (+39) 030 3501361. Fax: (+39) 02 700435727. E-mail: gfrisoni@fatebenefratelli.it Web: http://www.irccs-fatebenefratelli.it.

vs fronto-parietal cortex) interaction was detected (p=.002, ANOVA), in both early and late-onset patients (p<.05, ANOVA). We conclude that the ε4 allele modulates disease phenotype in AD, being associated with a pattern of differential temporal and fronto-parietal vulnerability.

Keywords

Apolipoprotein E; Alzheimer disease; cortical atrophy; computational neuroanatomy; MRI

Introduction

Alzheimer disease (AD) is a clinically heterogeneous disease, neuropathologically characterized by the accumulation of beta-amyloid plaques (Abeta) and neurofibrillary tangles (NFT) in the brain (Braak and Braak, 1991; Delacourte *et al*, 1999; Price and Morris, 1999; Thal *et al.*, 2002; Haroutunian *et al.*, 1999; Haroutunian *et al.*, 1998). Multiple genes and environmental factors are believed to be involved in the pathogenesis and development of the disorder, through a complex interplay still largely unknown. To date the major genetic risk factor known for AD is the ε4 allele of the Apolipoprotein E (*APOE*) gene, that is present with a higher frequency in AD subjects than in the normal population (Strittmatter *et al.*, 1993; Poirier *et al.*, 1993; Corder *et al.*, 1993; Tang *et al.*, 1998; Kukull *et al.*, 2002; Saunders *et al.*, 2000), and lowers the mean age at onset of the disease in a dose-dependent fashion (Poirier *et al.*, 1993; Blacker *et al.*, 1997; Meyer *et al.*, 1998; Goldstein *et al.*, 2001).

ApoE, the protein coded by the *APOE* gene, is a lipid transport protein implicated in maintenance and repair of neuronal cells (Mahley, 1988), and current *in vitro* and animal model data strongly suggest that the ε4 allele is less efficient than other isoforms in these functions, through mechanisms that involve neuronal growth (Nathan *et al.*, 1994), synaptic remodeling (Buttini *et al.*, 2002) and cholinergic function (Buttini *et al.*, 2002). The findings of faster brain atrophy rate (Chen *et al.*, 2007; Moffat *et al.*, 2000) and reduced hipppocampal volumes in healthy *APOE* ε4 carriers (Burggren *et al.*, 2008; Plassman *et al.*, 1997) seems to provide some *in vivo* evidence to the hypothesis of a pathogenic role of this allele in AD.

Less clear is whether the *APOE* ε4 allele has a role in modulating the expression of the disease. Post-mortem sudies reported a greater accumulation of AD pathological hallmarks in the neocortex of patients carrying the ε4 allele than those with no ε4 allele (Polvikoski *et al.*, 1995; Tiraboschi *et al.*, 2004; Nagy *et al.*, 1995). *In vivo* data however agree only partially with these findings. Indeed, they reported greater atrophy in carriers in specific regions of the brain, namely in the hippocampus, entorhinal cortex, and temporal pole (Hashimoto *et al.*, 2001; Geroldi *et al.*, 1999; Juottonen *et al.*, 1998; Lehtovirta *et al.*, 1995). Conversely, frontal (Geroldi *et al.*, 1999) and whole brain (Hashimoto *et al.*, 2001; Yasuda *et al.*, 1998) volumes seem to be relatively preserved in carriers than non-carriers. These findings, which seem to suggest a region-specific effect of the ε4 allele on brain atrophy rather than an overall greater disease severity in carriers (Hashimoto *et al.*, 2001), are not conclusive (Lehtovirta *et al.*, 1995; Jack *et al.*, 1998) and are limited by the small number of studies available.

Here we aim to resolve discordances in previous MRI studies by investigating *APOE*-related patterns of atrophy over the whole cortex. Compared with prior studies, which were based on manually outlined regions of interest, here we used a recently developed semi-automated MRI analysis technique (Thompson *et al.*, 2004) able to analyze the whole cortical mantle at thousands of homologous cortical points. We hypothesized that patterns of atrophy in AD patients would differ according to *APOE* genotype, with carriers showing greater involvement of the temporal lobe and non-carriers in the remainder of the cortex.

Methods

Participants and assessment

Subjects and genetic analysis—Subjects were recruited among ouptatients seen at the IRCCS Centro San Giovanni di Dio Fatebenefratelli (National Center for Alzheimer's Disease), in Brescia, Italy, between November 2002 and August 2005. Patients were enrolled in a study on neurodegenerative dementias aimed at detecting *in vivo* structural brain changes in various diseases, including Alzheimer's disease, frontotemporal dementia, Parkinson's disease, and dementia with Lewy bodies.

All patients underwent a standardized protocol including clinical, physical, neurological and neuropsychological evaluations. Each subject underwent MRI scan and laboratory exams, comprising complete blood count, chemistry profile, thyroid function, B12 and folic acid, and EKG. History was taken with a structured interview from patients' relatives (usually spouses or children), and was focused on those symptoms that might help in the differential diagnosis of the dementias (hallucinations, gait, language, and behavioural disturbances). Physical and neurologic examinations were performed by a geriatrician and a neurologist. Neuropsychological assessments were performed by a psychologist and included the evaluation of global cognitive status by Mini Mental State Examination (MMSE; Folstein *et al.*, 1975) and a neuropsychological battery assessing: verbal and non-verbal memory with Rey's word list immediate and delayed recall tests (Carlesimo *et al.*, 1996) and Rey figure delayed recall test (Caffarra *et al.*, 2002); attention and executive functions with the Trail Making Test (Reitan, 1958; Amodio *et al.*, 2002); language with the Phonological and Semantic fluency (Novelli *et al.*, 1986) and Token (De Renzi and Vignolo, 1962; Spinnler and Tognoni, 1987) tests; and visuo-spatial abilities with the Rey figure copy (Caffarra *et al.*, 2002). Severity of dementia was measured by the Clinical Dementia Rating score (Hughes *et al.*, 1982).

Genomic DNA was extracted from whole-blood samples of subjects according to standard procedures. *APOE* genotyping was carried out by PCR amplification and HhaI restriction enzyme digestion. The genotype was resolved on 4% Metaphor Gel (BioSpa, Italy) and visualized by ethidium bromide staining (Hixson and Vernier, 1990).

Twenty-nine patients were diagnosed with AD according to the NINCDS criteria (McKhann *et al.*, 1984) and were included in the study. Subjects were divided into two groups based on the presence (ε4+, n=15) or absence of the ε4 allele (ε4-, n=14). All the carriers were heterozygous (ε3ε4) for the ε4 allele whereas non-carriers were homozygous for the ε3 allele (ε3ε3) except for one subject who carried one ε2 allele.

A group of twenty-nine healthy persons was selected for comparisons with patients from those enrolled in a study on normal brain structure with MRI (ArchNor, Normative Archive of Structural Brain Magnetic Resonance Imaging), as described in detail elsewhere (Riello *et al.*, 2005). Subjects were outpatients of the Neuroradiology Units of the Città di Brescia Hospital in Brescia, undergoing brain MR scan for reasons other than memory disturbance, cognitive impairment, degenerative diseases, or head trauma, and whose MR scan was negative. In detail, clinical exclusion criteria were: MR scan for memory problems or cognitive impairment, MR scan for clinical suspicion of neuro-degenerative diseases (Parkinson's disease, progressive supranuclear palsy, Huntington's disease, multiple system atrophy, etc), patient undergoing MR for suspected stroke, history of transient ischemic attack or stroke, head trauma, alcohol and substance abuse, cortico-steroid therapy, and loss of weight greater than 5 kilograms in the last 6 months, and cognitive impairment on neuropsychological testing. Radiological exclusion criteria included: brain mass, white matter hyperintensities with signs and symptoms of multiple sclerosis, aneurysm larger than 10 mm, arteriovenous malformation, malformations of the central nervous system, enlarged cisterna magna, meningioma, severe

cerebrovascular disease, severe atrophy, large arachnoid cysts. Each subject underwent multidimensional assessment including clinical, neurological, and neuropsychological evaluation. Controls were matched 1:1 to AD patients according to age and sex.

Written informed consensus was obtained by all the subjects. No compensation was provided for study participation. The local ethics committee approved the study.

MR imaging

MR images were acquired at the Neuroradiology Unit of the Città di Brescia Hospital in Brescia with a Philips Gyroscan 1.0 T scanner. The acquisition protocol included T1-weighted and FLAIR sequences. High-resolution gradient echo T1-weighted sagittal 3D sequences were acquired using the following parameters: TR=20 ms, TE=5 ms, flip angle=30°, field of view=220 mm, acquisition matrix=256×256 and slice thickness=1.3 mm. Axial dual echo FLAIR sequences were acquired as follows: TR=5000 ms, TE=100 ms, flip angle=90°, field of view=230 mm, acquisition matrix=256×256, slice thickness=5 mm. T1-weighted images were used for cortical gray matter analyses, FLAIR sequences to assess subcortical cerebrovascular disease with the age-related white matter changes scale (Wahlund *et al.*, 2001, total score ranging between 0 and 30).

Cortical gray matter was studied using the cortical pattern matching technique developed at the Laboratory of Neuroimaging (LONI) of the University of California at Los Angeles (Thompson *et al.*, 2004).

Image preprocessing—The 3D images were reoriented along the AC-PC line and voxels below the cerebellum were removed with the MRIcro software (www.psychology.nottingham.ac.uk/staff/cr1/mricro.html). The anterior commissure was manually set as the origin of the spatial coordinates for an anatomical normalization algorithm implemented as part of the Statistical Parametric Mapping (SPM99) software package (www.fil.ion.ucl.ac.uk/spm). A 12-parameter affine transformation was used to normalize each image to a customized template in stereotaxic space, created from the MRI scans of the first 40 consecutively enrolled controls of the ArchNor project.

Cortical gray matter mapping—Individual brain masks for each hemisphere were extracted from normalized images with the automatic method EMS (expectation maximization segmentation; www.medicalimagecomputing.com/EMS) (Van Leemput *et al.*, 1999a; Van Leemput *et al.*, 1999b), visually inspected, and manually corrected with DISPLAY, a three-dimensional visualization program that enables simultaneous viewing of sagittal, coronal and axial slices of the brain (http://www.bic.mni.mcgill.ca/software/Display/Display.html), and allows the manual correction of errors between brain and non-brain tissue. The resulting masks were applied to normalized images to obtain ‘skull-stripped’ images of each hemisphere. A 3D model of hemispherical cortical surfaces was automatically extracted using intensity information (MacDonald *et al.*, 1994). Normalized images were segmented into gray matter (GM), white matter and cerebrospinal fluid using an algorithm that employs partial volume correction and bias field correction (Shattuck *et al.*, 2001).

Sulcal lines were traced by a single tracer (MP) on the cortical surfaces according to a previously validated anatomical delineation protocol (http://www.loni.ucla.edu/~khayashi/Public/medial_surface, http://www.loni.ucla.edu/~esowell/new_sulcvar.html). For each subject, 17 sulci were manually outlined on the lateral surface of each brain hemisphere, and a set of 12 sulci were traced on the medial surface; additional 3D lines were drawn to outline interhemispheric gyral limits. The reliability of manual outlining was assessed prior to experimental subject tracing with a standard protocol requiring the same rater to trace all lateral and medial sulci of 6 test

brains (Sowell *et al.*, 2002). At the end of the reliability phase, the mean 3D difference of the tracer from the gold standard was <3 mm everywhere for the medial sulci and <4.5 mm everywhere for the lateral sulci.

Sulcal curves and cortical surfaces were flattened and averaged across subjects to create a population specific template based on all subjects in the study (Thompson *et al.*, 2000). Averaged sulci were then used as landmarks to warp each subject's anatomy into the template. The same deformation was applied to the segmented images, thus allowing measurement of GM at thousands of homologous cortical locations. Gray matter density (GMD) was computed at each cortical point as the proportion of GM tissue classified as GM in a sphere centered at that point, with a radius of 15 mm, and then averaged within each group to obtain the GMD mean. All morphological measurements were performed without knowledge of genotype.

A map of the average percentage GM reduction was created for each AD patient group (ε4+ and ε4-) computing the ratio at each cortical point between the mean GMD value at that point in the patient group and the GMD mean of the controls. This ratio allows visualization of the relative deficit in GM of *APOE* groups as a proportion, or percentage, of the normal values seen in healthy controls. Differences in severity of GM reduction between ε4 carriers and non-carriers was assessed by computing at each cortical point, the absolute difference between percentage GM reduction in ε4+ and ε4-. The resulting map shows the percentage differences between *APOE* groups.

Gray matter loss in the Brodmann areas—A deformable Brodmann area (BA) atlas (Rasser *et al.*, 2004; Rasser *et al.*, 2005) was applied to the left and right hemisphere average models. Briefly, this involved the extraction of a three-dimensional model of the right cerebral hemisphere (MacDonald *et al.*, 1994) of the Colin27 single-subject average brain MRI template (Holmes *et al.*, 1998) followed by labeling with BA as delineated by the Caret software package (http://brainmap.wustl.edu/caret) (Van Essen *et al.*, 2001; Van Essen, 2002). BAs were then deformed to the average right and left hemisphere templates using cortical pattern matching, followed by the tabulation of each subject's average gray matter loss in each BA.

Statistical analysis

Cortical pattern matching analyses were carried out in two steps, first comparing each patient group (*APOE* ε4+ and *APOE* ε4-) with controls and then comparing ε4+ patients with ε4- patients. For the first set of comparisons, we ran a regression at each cortical point between GMD and diagnosis. For the second comparison, we ran a regression entering percentage GM deficits and *APOE* (ε4+ and ε4-) as binary variables. The *p*-values representing the significance of the variable effect (diagnosis, *APOE*) were mapped onto the whole cortex, after setting a significance threshold of $p=.05$. Overall *p*-values for the uncorrected statistical maps were computed by running permutation tests. This test computes the chance of the observed pattern occurring by accident by running $n=10{,}000$ permutations of the variables of interest (diagnosis and *APOE*) at a threshold of $p=.01$ (Thompson *et al.*, 2003).

In order to investigate the hypothesis of a region-specific effect of *APOE* on brain atrophy, we defined two regions on the BA atlas: (1) the temporal cortex, including the medial and lateral temporal lobes (superior, middle and inferior temporal gyrus, entorhinal, perirhinal and presubicular cortex, anterior temporal pole, and the fusiform gyrus), (2) the frontal and parietal neocortex (dorsolateral frontal and parietal cortex, orbitofrontal and subgenual cortex, anterior and posterior cingulate, and retrosplenial cortex; Figure 1). Main effect of *APOE* and cortical region on brain atrophy was investigated using an analysis of variance (ANOVA) model, where *APOE* (ε4+ *vs* ε4-) was the between-subject factor, region (temporal *vs* fronto-patietal cortex) was the within-subject factor, and percentage GM reduction was the dependent variable.

In order to assess whether age at onset of the disease had an impact on *APOE* effect, the analyses were repeated separately in early (<65 years, n=14) and late-onset (>65 years, n=15) patients, by comparing younger and older patients with their age-matched controls.

Results

Sociodemographic, clinical and neuropsychological data

Table 1 shows that *APOE* ε4 carriers and non-carrier patients were comparable in age (p=.358 on t-test), duration of dementia (p=.519), cerebrovascular burden (p=.203), and severity of the disease (p=.287 on chi-square), CDR scores being indicative of mild dementia in the most of the patients (Table 1). The ε4+ group had a greater proportion of women than ε4- (p=.009) and a lower educational level (p=.033; Table 1). Because some previous studies showed gender differences in gray matter volumes of healthy and AD subjects (Luders *et al*., 2006;Sowell *et al.*, 2007;Juottonen *et al.*, 1998), we replicated the analyses considering only women in order to ensure that these differences did not influence our results.

Controls were similar to ε4+ and ε4- patients with regard to age (p>.457 on t-test) and sex (p>.114 on chi-square test, Table 1). Years of education were comparable to that of ε4 non-carriers (p=.572) and higher than that of ε4 carriers (p<.001, Table 1). Global cognition was lower in patients compared with controls on the MMSE test (p<.001, Table 1) and in all the domains investigated by the neuropsychological battery (p<.038, Table 2). The degree of impairment was similar in ε4+ and ε4- patients on both MMSE scores (p=.862) and neuropsychological tests (p>.063; Table 2).

Cortical atrophy

Carriers and non-carriers vs controls—Both ε4+ and ε4- showed widespread cortical atrophy, involving most of the neocortex and sparing only the somatosensory and motor areas, the anterior cingulate gyrus, and the medial orbitofrontal cortex (thresholded at p<.01 uncorrected, Figure 2, top panel). In ε4+ patients, regions of significant atrophy mapped to the whole left and right temporal lobes, and to the occipital lobes, retrosplenial and posterior cingulate area (Figure 2, top left panel). The same regions were affected in the ε4- group, but involvement of the temporal lobe was less selective and conversely fronto-parietal atrophy appeared more diffuse (Figure 2, *top right panel*). Patterns of atrophy in the medial wall involved the posterior cingulate and retrosplenial cortex in both groups. The comparisons between patients and controls were highly significant after correction for multiple comparisons (p=.0001 for both ε4+ *vs* controls and ε4- *vs* controls, *permutation test*).

Percentage maps showed that overall severity of atrophy was similar, with ε4+ and ε4- showing an average GM reduction of 15% *vs* 14% in the left, and 16% *vs* 17% in the right hemisphere respectively (p>.80 on t-test). Regionally, the most severe GM reductions (>20%) in carriers were in the entorhinal cortex, anterior temporal pole, superior and middle temporal gyrus, and in the ventral and dorsal occipital lobe bilaterally (Figure 2, *bottom left panel*). Non-carriers were more severely affected bilaterally in the superior and middle frontal gyri, superior temporal gyrus, retrosplenial cortex, posterior cingulate and orbitofrontal medial right cortex (Figure 2, *bottom right panel*).

Carriers vs non-carriers—Direct comparisons between maps of percentage reduction in the ε4+ and ε4- groups revealed *APOE*-associated regions of atrophy. These analyses detected greater involvement of the medial and lateral temporal lobes, and of the right occipital pole (p<.01, uncorrected; Figure 3A, *left*) in the ε4+ group. The opposite effect (greater atrophy in non-carriers than carriers) was detected in the posterior cingulate and left lateral orbitofrontal cortex (p<.01 uncorrected; Figure 3A, *right*), and in the right dorsolateral cortex (p<.05

uncorrected). Differences significant at the uncorrected threshold of $p<.01$ corresponded to approximately 20% greater GM loss in the ε4 carriers than non-carriers (Figure 3B, *left*), whereas the opposite effect amounted to about 5-15% greater GM loss for non-carriers than carriers (Figure 3B, *right*). Statistical maps were not significant after controlling for multiple comparisons ($p>.33$; *permutation test*).

Analyses in Brodmann areas—GM loss in the temporal cortex region defined on BAs was 19% in carries and 16% in non-carriers relative to controls. In the fronto-parietal cortex, carriers exhibited a reduction of 14.5% *vs* 16% in non-carriers (Figure 3C). The ANOVA model showed in the whole sample a significant effect of region ($p=.001$) but not of *APOE* ($p=.740$) on GM loss. However, the interaction between *APOE* status and brain region was significant ($p=.002$,ANOVA; Figure 3C). When patients were separated into younger (ε4+: n=7, ε4-: n=7) and elderly (ε4+: n=8, ε4-: n=7), the interaction term in the ANOVA model was significant in both early ($p=.013$) and late-onset ($p=.050$) patients (Supplementary Figure S3).

The analyses carried out on the women samples (ε4+: n=14; ε4-: n=7) provided similar results. Patterns of atrophy remained highly significant in both carriers ($p=.0001$ on *permutation test*) and non-carriers ($p=.0003$) relative to controls, and confirmed that regional differences in GM loss between carriers and non-carriers mapped to the temporal and fronto-parietal cortex ($p<.01$ uncorrected). These differences were not significant after controlling for mutiple comparisons ($p>.57$, *permutation test*). The interaction term between *APOE* and region remained significant ($p=.008$, ANOVA. Supplementary materials).

Discussion

In the present study we found that *APOE* modulates AD pathology, the ε4 allele being associated with a pattern of increased susceptibility of the temporal cortex together with lower vulnerability in the fronto-parietal neocortical regions.

The finding of a significant interaction between *APOE* and region affected is in line with previous studies suggesting a region-specific effect *of APOE* on brain atrophy (Hashimoto *et al.*, 2001; Geroldi *et al.*, 1999), rather than greater disease severity in ε4 carriers. This modulating effect became evident when the analyses were driven by a-priori hypotheses consistent with previous data (Geroldi *et al.*, 1999; Hashimoto *et al.*, 2001). Although early studies did not assess the interaction between *APOE* and region, the findings of greater atrophy of the medial and lateral temporal cortex in ε4 carriers (Juottonen *et al.*, 1998; Lehtovirta *et al.*, 1995; Pennanen *et al.*, 2006; Hämäläinen *et al.*, 2008; Thomann *et al.*, 2008) together with milder involvement of whole brain volumes (Yasuda *et al.*, 1998; Lehtovirta *et al.*, 1995) are consistent with the hypothesis of a modulating effect of *APOE.* Lehtovirta did not actually report a significant difference between carriers and non-carriers in the frontal lobe, notwithstanding there was a trend for larger frontal volumes together with significantly smaller hippocampal volumes in carriers (Lehtovirta *et al.*, 1995). It is likely that the interaction effect detected here would be stronger if patients carrying two ε4 alleles were included, as *APOE* effect on brain atrophy has been reported to be proportional to allele dose (Yasuda *et al.*, 1998; Geroldi *et al.*, 1999). The lack of ε4 homozygous in our sample may indeed have reduced the statistical power of our findings.

The mechanism through which *APOE* affects regional atrophy might involve the role of apoE on the deposition of NFT. The temporal cortex is highly susceptible to NFT deposition whereas other neocortical areas are less vulnerable (Braak and Braak, 1991; Arnold *et al.*, 1991). An association between *APOE* ε4 and increased NFT deposition in the temporal cortex has been demonstrated *in vivo* in transgenic mice (Brecht *et al.*, 2004; Tesseur *et al.*, 2000), and from neuropathological examinations (Tiraboschi *et al.*, 2004; Nagy *et al.*, 1995). The effect of

APOE on atrophy in the temporal region might therefore be mediated by greater NFT deposition. Furthermore, the ε4 allele in the temporal lobe has been associated with impaired synaptic activity (Buttini *et al.*, 2002), reduced neurite outgrowth (Sun *et al.*, 1998), more severe Abeta deposition (Tiraboschi *et al.*, 2004; Nagy *et al.*, 1995) and cholinergic deficits (Buttini *et al.*, 2002). There are thus several possible mechanisms in addition to (or concurrent with) NFT deposition through which the ε4 allele may modulate temporal lobe atrophy in AD. Less straightforward is the interpretation of how *APOE* ε4 may be associated with a lesser degree of atrophy in the frontal and parietal neocortex; previous studies indeed reported a detrimental effect of the ε4 allele on Abeta deposition and cholinergic/synaptic activity in the fronto-parietal cortex as well (Buttini *et al.*, 2002; Soininen *et al.*, 1995; Beffert *et al.*, 1999). These data may thus indicate that the effect of *APOE* ε4 on atrophy may not be a simple consequence of Abeta deposition and of cholinergic/synaptic deficits. Furthermore, the relative preservation of the fronto-parietal cortex may alternatively suggest that *APOE* ε4 could be less detrimental in some respects. The ε4 allele indeed may be more efficient than other isoforms in aspects related to development, such as in promoting cognitive development (Yu *et al.*, 2000), although region-specific effects in the frontal and parietal neocortex have never been reported. A recent study has shown that – contrary to expectation – ε4 carriers had a better long-term outcomes after brain injury (Willemse-van Son *et al.*, 2008). These data, together with findings of longer survival, slower cognitive and functional decline, slower atrophy rate in AD patients who were ε4 carriers (Frisoni *et al.*, 1995; Hoyt *et al.*, 2005; Stern *et al.*, 1997; Sluimer *et al.*, 2008), may indicate that ε4 effect may be less detrimental than other isoforms in the long term (Teasdale, 2008). As experiments from basic and molecular studies are usually carried out over a relatively short period of time, they may lack the ability to address some aspects of the diseases that can be captured *in vivo*.

In the present study, carriers and non-carriers showed comparable cognitive deficits in all the domains investigated. This is to some extent in contrast with earlier studies reporting greater memory deficits in ε4 carriers (Smith *et al.*, 1998), and conversely more severe impairment in non-memory domains in AD patients lacking the ε4 allele (Lehtovirta *et al.*, 1996; Van Der Vlies *et al.*, 2007). The majority of previous studies that reported neuropsychological testing scores together with MRI indexes of atrophy found lower performance on memory tests in ε4 carriers (Lehtovirta *et al.*, 1995; Juottonen *et al.*, 1998), and one reported a significant association between number of ε4 alleles and score on attention and intelligence scales (Hashimoto *et al.*, 2001). A possible explanation for the discrepancies with previous studies may lie in differences in the sampling of the ε4 group: the association between the ε4 allele and atrophy seems to be gene-dose dependent (Yasuda *et al.*, 1998; Geroldi *et al.*, 1999), and previous studies included a subgroup of patients who were homozygous for the ε4 allele. Thus, the lack of patients carrying two ε4 alleles in our study may explain why we did not find a significant effect of *APOE* on cognition in our sample.

This study has both strengths and limitations. The major strength involves the spatial accuracy of our mapping technique that allows to compare anatomical features over the whole cortical mantle between subjects. Commonly used methods such as manual regions of interest tracing suffer the disadvantage of being spatially less detailed and typically they are strongly dependent on *a priori* hypothesis. As for limitations, although the sample size of our AD groups was comparable to that of previous studies, confirmation is required in larger samples to take into account factors that may have influenced our results to some degree, such as age, sex, and education differences. In this study indeed there was a larger proportion of women in carriers than non-carriers, and educational level differed between groups. A previous study (Juottonen *et al.*, 1998) reported that atrophy of the entorhinal cortex was more pronounced in female patients carrying at least one ε4 allele than in men. Conversely, some authors showed greater vulnerability of the frontal and parietal cortex in men and persons with a higher educational level (Kidron *et al.*, 1997). Although it is generally agreed that these factors may play a role

in modulating susceptibility to AD (Lahiri *et al.*, 2004; Azad *et al.*, 2007), it is less clear whether they can affect disease phenotype. In the present study, control subjects were overall matched to patients and this should have attenuated differences due to sociodemographic differences. Secondly, when we replicated the analyses excluding men, the results remained unchanged thus confirming that the effect observed was not due to differences in sex and/or education. Clearly, further studies including groups well-balanced in their sociodemographic features are recommended. Another limitation of the study is that *APOE* genotype was not available for all controls. Thus, we could not investigate changes modulated by *APOE* from those representing *APOE*-related morphological traits.

Conclusion

In the present study, we provided an independent confirmation of previous findings about a modulating effect of *APOE* on brain atrophy, the ε4 allele being associated with greater susceptibility of the temporal cortex, and conversely less vulnerability in the frontal-parietal cortex. These data suggest that the ε4 allele modulate AD phenotype. The mechanism underlying *APOE* ε4 effect on cortical atrophy however may be quite complex and involve several processes related to AD pathology.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

References

Amodio P, Wenin H, Del Piccolo F, Mapelli D, Montagnese S, Pellegrini A, Musto C, Gatta A, Umiltà C. Variability of trail making test, symbol digit test and line trait test in normal people. A normative study taking into account age-dependent decline and sociobiological variables. Aging Clin Exp Res 2002;14:117–131. [PubMed: 12092785]

Arnold SE, Hyman BT, Flory J, Damasio AR, Van Hoesen GW. The topographical and neuroanatomical distribution of neurofibrillary tangles and neuritic plaques in the cerebral cortex of patients with Alzheimer's disease. Cereb Cortex 1991;1:103–116. [PubMed: 1822725]

Azad NA, Al Bugami M, Loy-English I. Gender differences in dementia risk factors. Gend Med 2007;4:120–129. [PubMed: 17707846]

Beffert U, Cohn JS, Petit-Turcotte C, Tremblay M, Aumont N, Ramassamy C, Davignon J, Poirier J. Apolipoprotein E and beta-amyloid levels in the hippocampus and frontal cortex of Alzheimer's disease subjects are disease-related and apolipoprotein E genotype dependent. Brain Res 1999;843:87–94. [PubMed: 10528114]

Blacker D, Haines JL, Rodes L, Terwedow H, Go RC, Harrell LE, Perry RT, Bassett SS, Chase G, Meyers D, Albert MS, Tanzi R. ApoE-4 and age at onset of Alzheimer's disease: the NIMH Genetics Initiative. Neurology 1997;48:139–147. [PubMed: 9008509]

Braak H, Braak E. Neuropathological stageing of Alzheimer-related changes. Acta Neuropathol 1991;82:239–259. [PubMed: 1759558]

Brecht WJ, Harris FM, Chang S. Neuron-specific apolipoprotein E4 proteolysis is associated with increased tau phosphorylation in brains of transgenic mice. J Neurosci 2004;24:2527–2534. [PubMed: 15014128]

Burggren AC, Zeineh MM, Ekstrom AD, Braskie MN, Thompson PM, Small GW, Bookheimer SY. Reduced cortical thickness in hippocampal subregions among cognitively normal apolipoprotein E e4 carriers. Neuroimage 2008;41:1177–1183. [PubMed: 18486492]

Buttini M, Yu GQ, Shockley K, Huang Y, Jones B, Masliah E, Mallory M, Yeo T, Longo FM, Mucke L. Modulation of Alzheimer-like synaptic and cholinergic deficits in transgenic mice by human apolipoprotein E depends on isoform, aging, and overexpression of amyloid beta peptides but not on plaque formation. J Neurosci 2002;22:10539–10548. [PubMed: 12486146]

Caffarra P, Vezzadini G, Dieci F, Zonato F, Venneri A. Rey-Osterrieth complex figure: normative values in an Italian population sample. Neurol Sci 2002;22:443–447. [PubMed: 11976975]

Carlesimo GA, Caltagirone C, Gainotti G. The Mental Deterioration Battery: normative data, diagnostic reliability and qualitative analyses of cognitive impairment. The Group for the Standardization of the Mental Deterioration. Battery. Eur Neurol 1996;36:378–384. [PubMed: 8954307]

Chen K, Reiman EM, Alexander GE, Caselli RJ, Gerkin R, Bandy D, Domb A, Osborne D, Fox N, Crum WR, Saunders AM, Hardy J. Correlations between apolipoprotein E epsilon4 gene dose and whole brain atrophy rates. Am J Psychiatry 2007;164:916–921. [PubMed: 17541051]

Corder EH, Saunders AM, Strittmatter WJ, Schmechel DE, Gaskell PC, Small GW, Roses AD, Haines JL, Pericak-Vance MA. Gene dose of apolipoprotein E type 4 allele and the risk of Alzheimer's disease in late onset families. Science 1993;261:921–923. [PubMed: 8346443]

Delacourte A, David JP, Sergeant N, Buée L, Wattez A, Vermersch P, Ghozali F, Fallet-Bianco C, Pasquier F, Lebert F, Petit H, Di Menza C. The biochemical pathway of neurofibrillary degeneration in aging and Alzheimer's disease. Neurology 1999;52:1158–1165. [PubMed: 10214737]

De Renzi E, Vignolo LA. The token test: a sensitive test to detect receptive disturbances in aphasia. Brain 1962;85:665–678. [PubMed: 14026018]

Folstein MF, Folstein SE, McHugh PR. “Mini-mental State”. A practical method for grading the cognitive state of patients for the clinician. Psychiatr Res 1975;12:189–198.

Frisoni GB, Govoni S, Geroldi C, Bianchetti A, Calabresi L, Franceschini G, Trabucchi M. Gene dose of the epsilon 4 allele of apolipoprotein E and disease progression in sporadic late-onset Alzheimer's disease. Ann Neurol 1995;37:596–604. [PubMed: 7755354]

Geroldi C, Pihlajamäki M, Laakso MP, DeCarli C, Beltramello A, Bianchetti A, Soininen H, Trabucchi M, Frisoni GB. *APOE*-epsilon4 is associated with less frontal and more medial temporal lobe atrophy in AD. Neurology 1999;53:1825–1832. [PubMed: 10563634]

Goldstein FC, Ashley AV, Gearing M, Hanfelt J, Penix L, Freedman LJ, Levey AI. Apolipoprotein E and age at onset of Alzheimer's disease in African American patients. Neurology 2001;57:1923–1925. [PubMed: 11723294]

Hashimoto M, Yasuda M, Tanimukai S, Matsui M, Hirono N, Kazui H, Mori E. Apolipoprotein E epsilon 4 and the pattern of regional brain atrophy in Alzheimer's disease. Neurology 2001;57:1461–1466. [PubMed: 11673590]

Holmes CJ, Hoge R, Collins L, Woods R, Toga AW, Evans AC. Enhancement of MR images using registration for signal averaging. J Comput Assist Tomogr 1998;22:324–333. [PubMed: 9530404]

Hoyt BD, Massman PJ, Schatschneider C, Cooke N, Doody RS. Individual growth curve analysis of *APOE* epsilon 4-associated cognitive decline in Alzheimer disease. Arch Neurol 2005;62:454–459. [PubMed: 15767511]

Hughes CP, Berg L, Danziger WL, Coben LA, Martin RL. A new clinical scale for the staging of dementia. Br J Psychiatry 1982;140:566–572. [PubMed: 7104545]

Jack CR Jr, Petersen RC, Xu YC, O'Brien PC, Waring SC, Tangalos EG, Smith GE, Ivnik RJ, Thibodeau SN, Kokmen E. Hippocampal atrophy and apolipoprotein E genotype are independently associated with Alzheimer's disease. Ann Neurol 1998;43:303–310. [PubMed: 9506546]

Juottonen K, Lehtovirta M, Helisalmi S, Riekkinen PJ, Soininen H. Major decrease in the volume of the entorhinal cortex in patients with Alzheimer's disease carrying the apolipoprotein E ε4 allele. J Neurol Neurosurg Psychiatry 1998;65:322–327. [PubMed: 9728943]

Hämäläinen A, Grau-Olivares M, Tervo S, Niskanen E, Pennanen C, Huuskonen J, Kivipelto M, Hanninen T, Tapiola M, Vanhanen M, Hallikainen M, Helkala EL, Nissinen A, Vanninen RL, Soininen H. Apolipoprotein E epsilon 4 allele is associated with increased atrophy in progressive mild cognitive impairment: a voxel- ased morphometric study. Neurodegener Dis 2008;5:186–189. [PubMed: 18322386]

Haroutunian V, Perl DP, Purohit DP, Marin D, Khan K, Lantz M, Davis KL, Mohs RC. Regional distribution of neuritic plaques in the nondemented elderly and subjects with very mild Alzheimer disease. Arch Neurol 1998;55:1185–1191. [PubMed: 9740112]

Haroutunian V, Purohit DP, Perl DP, Marin D, Khan K, Lantz M, Davis KL, Mohs RC. Neurofibrillary tangles in nondemented elderly subjects and mild Alzheimer disease. Arch Neurol 1999;56:713–718. [PubMed: 10369312]

Hixson JE, Vernier DT. Restriction isotyping of human apolipoprotein E by gene amplification and cleavage with HhaI. J Lipid Res 1990;31:545–548. [PubMed: 2341813]

Kidron D, Black SE, Stanchev P, Buck B, Szalai JP, Parker J, Szekely C, Bronskill MJ. Quantitative MR volumetry in Alzheimer's disease. Topographic markers and the effects of sex and education. Neurology 1997;49:1504–1512. [PubMed: 9409337]

Kukull WA, Higdon R, Bowen JD, McCormick WC, Teri L, Schellenberg GD, van Belle G, Jolley L, Larson EB. Dementia and Alzheimer disease incidence: a prospective cohort study. Arch Neurol 2002;59:1737–1746. [PubMed: 12433261]

Lahiri DK, Sambamurti K, Bennett DA. Apolipoprotein gene and its interaction with the environmentally driven risk factors: molecular, genetic and epidemiological studies of Alzheimer's disease. Neurobiol Aging 2004;25:651–660. [PubMed: 15172744]

Lehtovirta M, Laakso MP, Soininen H, Helisalmi S, Mannermaa A, Helkala EL, Partanen K, Ryynänen M, Vainio P, Hartikainen P, Riekkinen PJ. Volumes of hippocampus, amygdala and frontal lobe in Alzheimer patients with different apolipoprotein E genotypes. Neuroscience 1995;67:65–72. [PubMed: 7477910]

Lehtovirta M, Soininen H, Helisalmi S, Mannermaa A, Helkala EL, Hartikainen P, Hänninen T, Ryynänen M, Riekkinen PJ. Clinical and neuropsychological characteristics in familial and sporadic Alzheimer's disease: Relation to apolipoprotein E polymorphism. Neurology 2006;43:416–419.

Luders E, Narr KL, Thompson PM, Rex DE, Woods RP, Deluca H, Jancke L, Toga AW. Gender effects on cortical thickness and the influence of scaling. Hum Brain Mapp 2006;27:314–324. [PubMed: 16124013]

MacDonald D, Avis D, Evans A. Multiple surface identification and matching in magnetic resonance imaging. Proc SPIE 1994;2359:160–169.

McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM. Clinical diagnosis of Alzheimer's disease: report of the NINCDSADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. Neurology 1984;34:939–944. [PubMed: 6610841]

Mahley RW. Apolipoprotein E: cholesterol transport protein with expanding role in cell biology. Science 1988;240:622–630. [PubMed: 3283935]

Meyer MR, Tschanz JT, Norton MC, Welsh-Bohmer KA, Steffens DC, Wyse BW, Breitner JC. *APOE* genotype predicts when—not whether—one is predisposed to develop Alzheimer disease. Nat Genet 1998;19:321–322. [PubMed: 9697689]

Moffat SD, Szekely CA, Zonderman AB, Kabani NJ, Resnick SM. Longitudinal change in hippocampal volume as a function of apolipoprotein E genotype. Neurology 2000;55:134–136. [PubMed: 10891924]

Nagy Z, Esiri MM, Jobst KA, Johnston C, Litchfield S, Sim E, Smith AD. Influence of the apolipoprotein E genotype on amyloid deposition and neurofibrillary tangle formation in Alzheimer's disease. Neuroscience 1995;69:757–761. [PubMed: 8596645]

Nathan BP, Bellosta S, Sanan DA, Weisgraber KH, Mahley RW, Pitas RE. Differential effects of apolipoproteins E3 and E4 on neuronal growth in vitro. Science 1994;264:850–852. [PubMed: 8171342]

Novelli G, Papagno C, Capitani E, Laiacona M, Vallar G, Cappa SF. Tre test clinici di ricerca e produzione lessicale. Taratura su soggetti normali. Arch Psicol Neurol Psichiatr 1986;47:477–506.

Pennanen C, Testa C, Boccardi M, Laakso MP, Hallikainen M, Helkala EL, Hanninen T, Kivipelto M, Kononen M, Nissinen A, Tervo S, Vanhanen M, Vanninen R, Frisoni GB, Soininen H. The effect of apolipoprotein polymorphism on brain in mild cognitive impairment: a voxel-based morphometric study. Dement Geriatr Cogn Disord 2006;22:60–66. [PubMed: 16682795]

Plassman BL, Welsh-Bohmer KA, Bigler ED, Johnson SC, Anderson CV, Helms MJ, Saunders AM, Breitner JC. Apolipoprotein E epsilon 4 allele and hippocampal volume in twins with normal cognition. Neurology 1997;48:985–989. [PubMed: 9109888]

Polvikoski T, Sulkava R, Haltia M, Kainulainen K, Vuorio A, Verkkoniemi A, Niinistö L, Halonen P, Kontula K. Apolipoprotein E, dementia, and cortical deposition of beta-amyloid protein. N Engl J Med 1995;333:1242–1247. [PubMed: 7566000]

Poirier J, Davignon J, Bouthillier D, Kogan S, Bertrand P, Gauthier S. Apolipoprotein E polymorphism and Alzheimer's disease. Lancet 1993;342:697–699. [PubMed: 8103819]

Price JL, Morris JC. Tangles and plaques in nondemented aging and “preclinical” Alzheimer's disease. Ann Neurol 1999;45:358–368. [PubMed: 10072051]

Rasser, PE.; Johnston, PJ.; Ward, PB.; Thompson, PM. A deformable Brodmann area atlas. IEEE International Symposium on Biomedical Imaging: Macro to Nano; Arlington,VA, USA. IEEE International Symposium on 15-18 April 2004; 2004. p. 400-403.

Rasser PE, Johnston P, Lagopoulos J, Ward P, Schall U, Thienel R, Bender S, Toga A, Thompson PM. Functional MRI BOLD response to Tower of London performance of first-episode schizophrenia patients using cortical pattern matching. Neuroimage 2005;26:941–951. [PubMed: 15955504]

Reitan RM. Validity of the trailmaking test as an indication of organic brain damage. Percept Mot Skills 1958;8:271–276.

Riello R, Sabattoli F, Beltramello A, Bonetti M, Bono G, Falini A, Magnani G, Minonzio G, Piovan E, Alaimo G, Ettori M, Galluzzi S, Locatelli E, Noiszewska M, Testa C, Frisoni GB. Brain volumes in healthy adults aged 40 years and over: a voxel-based morphometry study. Aging Clin Exp Res 2005;17:329–336. [PubMed: 16285200]

Saunders AM, Trowers MK, Shimkets RA, Blakemore S, Crowther DJ, Mansfield TA, Wallace DM, Strittmatter WJ, Roses AD. The role of apolipoprotein E in Alzheimer's disease: pharmacogenomic target selection. Biochim Biophys Acta 2000;1502:85–94. [PubMed: 10899434]

Shattuck DW, Sandor-Leahy SR, Schaper KA, Rottenberg DA, Leahy RM. Magnetic resonance image tissue classification using a partial volume model. Neuroimage 2001;13:856–876. [PubMed: 11304082]

Sluimer JD, Vrenken H, Blankenstein MA, Fox NC, Scheltens P, Barkhof F, van der Flier WM. Whole-brain atrophy rate in Alzheimer disease: identifying fast progressors. Neurology 2008;70:1836–1841. [PubMed: 18458218]

Smith GE, Bohac DL, Waring SC, Kokmen E, Tangalos EG, Ivnik RJ, Petersen RC. Apolipoprotein E genotype influences cognitive ‘phenotype’ in patients with Alzheimer's disease but not in healthy control subjects. Neurology 1998;50:355–362. [PubMed: 9484353]

Soininen H, Kosunen O, Helisalmi S, Mannermaa A, Paljärvi L, Talasniemi S, Ryynänen M, Riekkinen P. A severe loss of choline acetyltransferase in the frontal cortex of Alzheimer patients carrying apolipoprotein epsilon 4 allele. Neurosci Lett 1995;187:79–82. [PubMed: 7783963]

Sowell ER, Thompson PM, Rex D, Kornsand D, Tessner KD, Jernigan TL, Toga AW. Mapping sulcal pattern asymmetry and local cortical surface GM distribution in vivo: maturation in perisylvian cortices. Cereb Cortex 2002;12:17–26. [PubMed: 11734529]

Sowell ER, Peterson BS, Kan E, Woods RP, Yoshii J, Bansal R, Xu D, Zhu H, Thompson PM, Toga AW. Sex differences in cortical thickness mapped in 176 healthy individuals between 7 and 87 years of age. Cereb Cortex 2007;17:1550–1560. [PubMed: 16945978]

Spinnler H, Tognoni G. Standardizzazione e taratura italiana di test neuropsicologici. Ital J Neurol Sci 1987;6

Stern Y, Brandt J, Albert M, Jacobs DM, Liu X, Bell K, Marder K, Sano M, Albert S, Del-Castillo Castenada C, Bylsma F, Tycko B, Mayeux R. The absence of an apolipoprotein epsilon4 allele is associated with a more aggressive form of Alzheimer's disease. Ann Neurol 1997;41:615–620. [PubMed: 9153523]

Strittmatter WJ, Saunders AM, Schmechel D, Pericak-Vance M, Enghild J, Salvesen GS, Roses AD. Apolipoprotein E: high-avidity binding to beta-amyloid and increased frequency of type 4 allele in late-onset familial Alzheimer disease. Proc Natl Acad Sci USA 1993;90:1977–1981. [PubMed: 8446617]

Sun Y, Wu S, Bu G, Onifade MK, Patel SN, LaDu MJ, Fagan AM, Holtzman DM. Glial fibrillary acidic protein-apolipoprotein E (apoE) transgenic mice: astrocyte-specific expression and differing biological effects of astrocyte-secreted apoE3 and apoE4 lipoproteins. J Neurosci 1998;18:3261–3272. [PubMed: 9547235]

Tang MX, Stern Y, Marder K, Bell K, Gurland B, Lantigua R, Andrews H, Feng L, Tycko B, Mayeux R. The APOE-epsilon4 allele and the risk of Alzheimer disease among African Americans, whites, and Hispanics. JAMA 1998;279:751–755. [PubMed: 9508150]

Teasdale TW. The apolipoprotein-e4 gene: always harmful? JNNP 2008;79:364–365.

Tesseur I, Van Dorpe J, Spittaels K, Van den Haute C, Moechars D, Van Leuven F. Expression of human apolipoprotein E4 in neurons causes hyperphosphorylation of protein tau in the brains of transgenic mice. Am J Pathol 2000;156:951–964. [PubMed: 10702411]

Thal DR, Rüb U, Orantes M, Braak H. Phases of A beta-deposition in the human brain and its relevance for the development of AD. Neurology 2002;58:1791–1800. [PubMed: 12084879]

Thomann PA, Roth AS, Dos Santos V, Toro P, Essig M, Schröder J. Apolipoprotein E Polymorphism and Brain Morphology in Mild Cognitive Impairment. Dement Geriatr Cogn Disord 2008;26:300–305. [PubMed: 18843182]

Thompson PM, Woods RP, Mega MS, Toga AW. Mathematical/computational challenges in creating deformable and probabilistic atlases of the human brain. Hum Brain Mapp 2000;9:81–92. [PubMed: 10680765]

Thompson PM, Hayashi KM, Sowell ER, Gogtay N, Giedd JN, Rapoport JL, de Zubicaray GI, Janke AL, Rose SE, Semple J, Doddrell DM, Wang Y, van Erp TG, Cannon TD, Toga AW. Mapping cortical change in Alzheimer's disease, brain development, and schizophrenia. Neuroimage 2004;23:S2–18. [PubMed: 15501091]

Thompson PM, Hayashi KM, de Zubicaray G, Janke AL, Rose SE, Semple J, Herman D, Hong MS, Dittmer SS, Doddrell DM, Toga AW. Dynamics of gray matter loss in Alzheimer's disease. J Neurosci 2003;23:994–1005. [PubMed: 12574429]

Tiraboschi P, Hansen LA, Masliah E, Alford M, Thal LJ, Corey-Bloom J. Impact of *APOE* genotype on neuropathologic and neurochemical markers of Alzheimer disease. Neurology 2004;62:1977–1983. [PubMed: 15184600]

van der Vlies AE, Pijnenburg YA, Koene T, Klein M, Kok A, Scheltens P, van der Flier WM. Cognitive impairment in Alzheimer's disease is modified by *APOE* genotype. Dement Geriatr Cogn Disord 2007;24:98–103. [PubMed: 17596691]

Van Essen DC, Dickson J, Harwell J, Hanlon D, Anderson CH, Drury HA. An Integrated Software System for Surface-based Analyses of Cerebral Cortex. Journal of American Medical Informatics Association 2001;8:443–459.

Van Essen DC. Windows on the brain. The emerging role of atlases and databases in neuroscience. Curr Op Neurobiol 2002;12:574–579. [PubMed: 12367638]

Van Leemput K, Maes F, Vandermeulen D, Suetens P. Automated model-based bias field correction of MR images of the brain. IEEE Trans Med Imaging 1999a;18:885–896. [PubMed: 10628948]

Van Leemput K, Maes F, Vandermeulen D, Suetens P. Automated model-based tissue classification of MR images of the brain. IEEE Trans Med Imaging 1999b;18:897–908. [PubMed: 10628949]

Yasuda M, Mori E, Kitagaki H, Yamashita H, Hirono N, Shimada K, Maeda K, Tanaka C. Apolipoprotein E ε4 allele and whole brain atrophy in late-onset Alzheimer's disease. Am J Psychiatry 1998;155:779–784. [PubMed: 9619150]

Yu YW, Lin CH, Chen SP, Hong CJ, Tsai SJ. Intelligence and event-related potentials for young female human volunteer apolipoprotein E epsilon4 and non-epsilon4 carriers. Neurosci Lett 2000;294:179–181. [PubMed: 11072144]

Wahlund LO, Barkhof F, Fazekas F, Bronge L, Augustin M, Sjogren M, Wallin A, Ader H, Leys D, Pantoni L, Pasquier F, Erkinjuntti T, Scheltens P, European Task Force on Age-Related White Matter Changes. A new rating scale for age-related white matter changes applicable to MRI and CT. Stroke 2001;32:1318–1322. [PubMed: 11387493]

Willemse-van Son AH, Ribbers GM, Hop WC, van Duijn CM, Stam HJ. Association between apolipoprotein-epsilon4 and long-term outcome after traumatic brain injury. JNNP 2008;79:426–430.

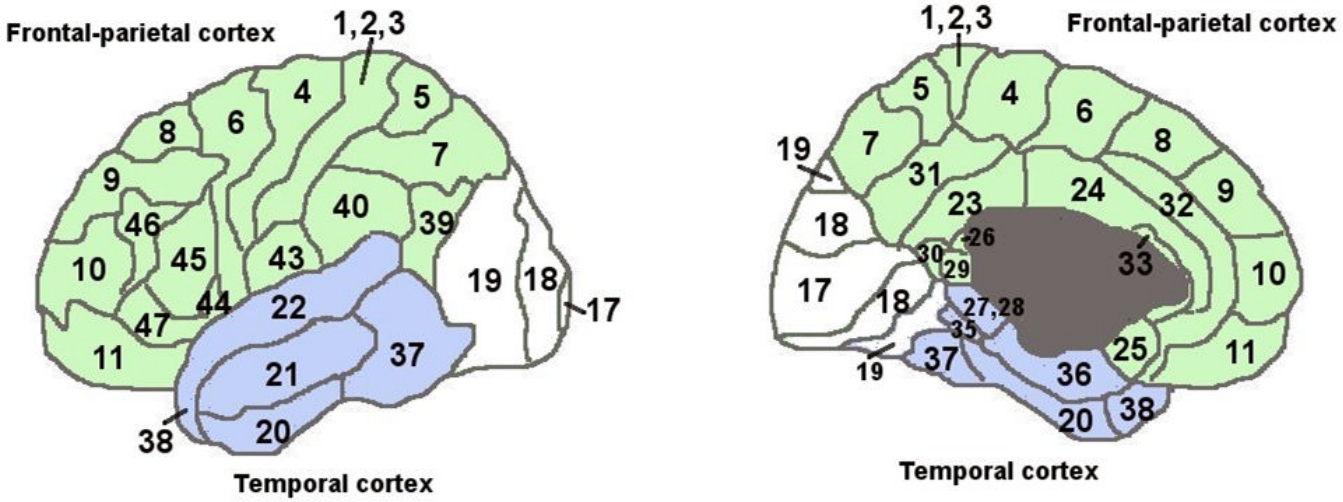

Figure 1.

(*Top*) 2D representation of the deformable atlas used to compute gray matter reduction in the Brodmann areas (Rasser *et al.*, 2004; Rasser *et al.*, 2005). (*Bottom*) The two regions-of-interest used to test *APOE* regional effect delineated on BA atlas: the temporal cortex (*blue colour*) and the fronto-parietal neocortex (*green colour*). See text for details.

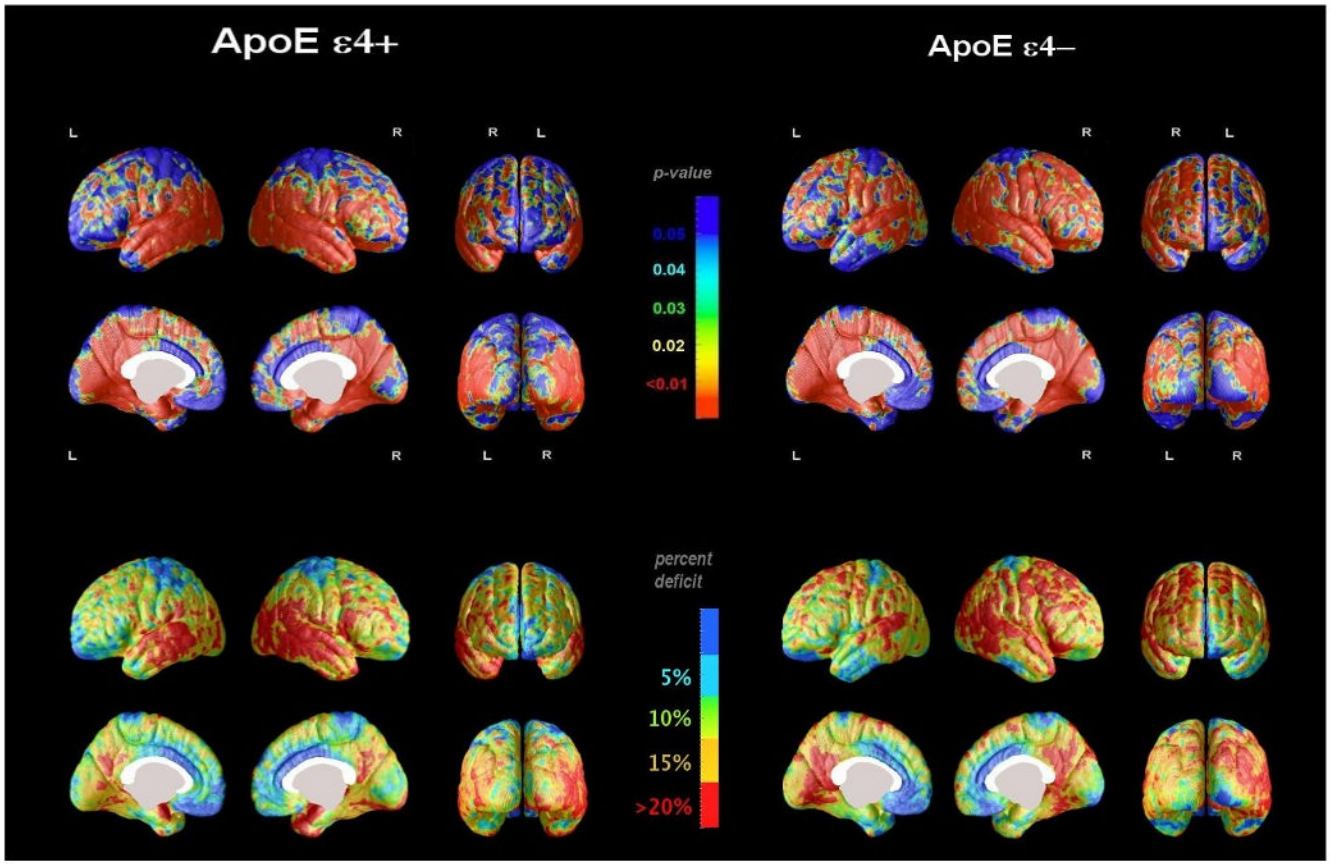

Figure 2.

Patterns of GM loss in Alzheimer disease patients carrying (ε4+) and non-carrying (ε4-) the *APOE* ε4 allele compared with age-matched controls. *Top*: statistical maps, showing areas of significantly reduced cortical GM in (*a*) ε4+ *vs* controls and (*b*) ε4- *vs* controls. Red regions correspond to a threshold of $p<.01$ uncorrected. Maps were significant after correction for multiple comparisons ($p=.0001$ for both comparisons, *permutation test*). *Bottom*: GM reduction in (*c*) ε4+ and (*d*) ε4- compared with controls, expressed as a percentage of the difference in GM between patients and controls. Values greater than 15% (yellow to red regions) denote statistically significant atrophic areas and red regions correspond to areas of severe GM reduction (greater than 25%).

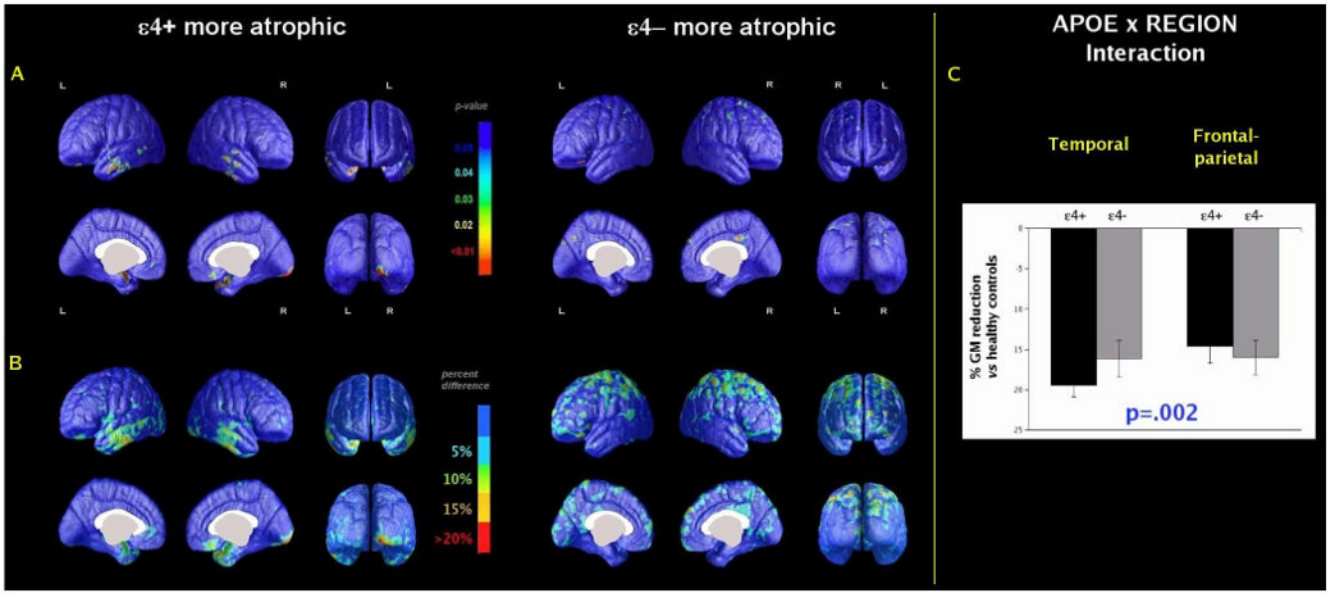

Figure 3.
(A-B) *APOE*-related patterns of cortical atrophy. The maps show regions more (*left*) and less (*right*) vulnerable to atrophy in ε4+ patients. *Top*: significance maps for the comparisons (*left*) ε4+ *vs* ε4-, and (*right*) ε4- *vs* ε4+. Red regions correspond to a threshold of $p<.01$ uncorrected. Maps were not significant after correction for multiple comparisons at a threshold of $p<.01$ ($p>.33$, *permutation test*). *Bottom*: Extent of increased (*left*) and reduced (*right*) vunerability in ε4+, expressed as a percentage of the difference in GM reduction between carriers and non-carriers. (C) Graph showing the interaction between *APOE* status (ε4+ *vs* ε4-) and cortical region (temporal *vs* fronto-parietal neocortex) in AD patients. *P* denotes significance of the interaction on ANOVA. Error bars denote standard errors.

Table 1

Sociodemographic, clinical and volumetric data of Alzheimer's disease patient carriers (ε4+) and non carriers (ε4-) of the *APOE* ε4 allele and age-matched controls.

		Controls	Alzheimer's patients		
		n=29	**ε4- n=14**	**ε4+ n=15**	***p***
Age (years)		69.7 (8.7)	68.6 (8.7)	71.8 (9.8)	.358
Sex (females)		21 (72%)	7 (50%)	14 (93%)	.009
Education (years)		9 (4)	8 (6)	4 (1)	.033
Mini-Mental State Exam		28.3 (1.2)	20.0 (4.8)	20.3 (3.3)	.862
Clinical dementia rating	0.5	---	4 (29%)	1 (7%)	
	1	---	9 (64%)	13 (86%)	
	2	---	1 (7%)	1 (7%)	.287
Disease duration (years)		---	3.1 (1.7)	3.5 (1.5)	.519
White matter disease[§]		2.0 (2.4)	2.2 (2.2)	3.8 (4.0)	.203

Values denotes mean (standard deviation) or number (percentage). *p* denotes significance of differences between ε4+ and ε4- on χ^2 test for dichotomous variables, and Student *t*-test or Mann-Whitney *U*-test -depending on the samples distribution- for continuous variables. ε4+ and ε4- patients differ from controls in their MMSE score ($p<.001$ on *t*-test). Educational level is lower in ε4+ that in controls ($p<.001$ on Mann-Whitney). There are no dfferences between patients and controls relatively to sex ($p>.103$ on χ^2 test) and white matter disease ($p>.135$ on *t*-test).

[§]on the Age-Related White Matter Changes Scale (Wahlund *et al.*, 2001)

Table 2

Neuropsychological features of Alzheimer's disease patients carrying (ε4+) and non carrying (ε4-) the *APOE* ε4 allele and control subjects. Test scores are age-, sex-, and education-adjusted.

	Controls	Alzheimer's patients		
	n=29	ε4- n=14	ε4+ n=15	*p*
Memory				
Rey list immediate recall	47 (7)	25 (9)	22 (8)	.357
Rey list delayed recall	11 (2.5)	2.9 (1.8)	2.7 (1.5)	.698
Rey figure recall	21 (6)	5 (5)	8 (2)	.093
Language				
Letter	35 (10)	28 (9)	22 (8)	.063
Category	42 (7)	25 (9)	25 (6)	.970
Token test	32 (3)	27 (7)	26 (6)	.627
Visuo-spatial abilities				
Rey figure copy	36 (1)	13 (14)	10 (9)	.564
Attention and executive functions				
Trail Making Test A	24 (13)	172 (122)	208 (107)	.398
Trail Making Test B	53 (43)	330 (148)	367 (107)	.455
Trail Making Test B-A	28 (38)	157 (99)	149 (93)	.827

Values denotes mean (standard deviation). *p* denotes significance on Student *t*-test between ε4 carriers and non-carriers. ε4+ and ε4- patients perform significantly poorer than controls in memory ($p<.001$), language ($p<.002$ and $p<.037$), visuo-spatial abilities ($p<.001$), and attention-executive functions ($p<.001$).