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Authors

Donix, Markus

Burggren, Alison C

Scharf, Maria

et al.

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# APOE associated hemispheric asymmetry of entorhinal cortical thickness in aging and Alzheimer's disease

Markus Donix [a,b,*,1], Alison C. Burggren [c,d,1], Maria Scharf [a,b], Kira Marschner [a,b], Nanthia A. Suthana [c,e], Prabha Siddarth [d], Allison K. Krupa [c,d], Michael Jones [c,d], Laurel Martin-Harris [c,d], Linda M. Ercoli [d], Karen J. Miller [d], Annett Werner [h], Rüdiger von Kummer [h], Cathrin Sauer [a], Gary W. Small [d,g], Vjera A. Holthoff [a,b,1], Susan Y. Bookheimer [c,d,f,1]

[a] Department of Psychiatry and Psychotherapy, Division of Old Age Psychiatry and Cognitive Neuropsychiatry, Faculty of Medicine Carl Gustav Carus, Technische Universität Dresden, 01307 Dresden, Germany
[b] DZNE, German Center for Neurodegenerative Diseases, Dresden, Germany
[c] David Geffen School of Medicine at UCLA, Center for Cognitive Neurosciences, Semel Institute, Los Angeles, CA 90095, USA
[d] David Geffen School of Medicine at UCLA, Department of Psychiatry and Biobehavioral Sciences, Semel Institute, Los Angeles, CA 90095, USA
[e] David Geffen School of Medicine at UCLA, Department of Neurosurgery, Los Angeles, CA 90095, USA
[f] David Geffen School of Medicine at UCLA, Department of Psychology, Los Angeles, CA 90095, USA
[g] UCLA Longevity Center, CA 90095, USA
[h] Department of Neuroradiology, Faculty of Medicine Carl Gustav Carus, Technische Universität Dresden, 01307 Dresden, Germany

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ABSTRACT

Across species structural and functional hemispheric asymmetry is a fundamental feature of the brain. Environmental and genetic factors determine this asymmetry during brain development and modulate its interaction with brain disorders. The e4 allele of the apolipoprotein E gene (APOE-4) is a risk factor for Alzheimer's disease, associated with regionally specific effects on brain morphology and function during the life span. Furthermore, entorhinal and hippocampal hemispheric asymmetry could be modified by pathology during Alzheimer's disease development. Using high-resolution magnetic resonance imaging and a cortical unfolding technique we investigated whether carrying the APOE-4 allele influences hemispheric asymmetry in the entorhinal cortex and the hippocampus among patients with Alzheimer's disease as well as in middle-aged and older cognitively healthy individuals. APOE-4 carriers showed a thinner entorhinal cortex in the left hemisphere when compared with the right hemisphere across all participants. Non-carriers of the allele showed this asymmetry only in the patient group. Cortical thickness in the hippocampus did not vary between hemispheres among APOE-4 allele carriers and non-carriers. The APOE-4 allele modulates hemispheric asymmetry in entorhinal cortical thickness. Among Alzheimer's disease patients, this asymmetry might be less dependent on the APOE genotype and a more general marker of incipient disease pathology.



## 1. Introduction

Neuropathological hallmarks of Alzheimer's disease, beta amyloid plaques and neurofibrillary tangles, can be found in the brain decades before the onset of clinical symptoms (Braak and Braak, 1995). In vivo detection of pathological changes that are closely associated with future cognitive deterioration could be critical for targeting novel therapies to those persons most likely to benefit from intervention. The spatial distribution of intraneuronal tangle pathology, rather than the pattern of extracellular amyloid deposition, is associated with neuronal loss and cognitive dysfunction (Gomez-Isla et al., 1997; Petersen et al., 2006). In fact, these neurofibrillary tangles first occur in the transentorhinal region before spreading to the hippocampus and other neighboring cortices (Braak and Braak, 1995). Multiple imaging metrics now exist for the identification of these neuropathological markers both before the onset, and during the progression of Alzheimer's disease. Modern methods include positron emission tomography (PET), using radioactive ligands that bind to plaques and tangles in the brain (Protas et al., 2010), magnetic resonance imaging (MRI) of brain structure (Donix et al., 2010a), function (Xu et al., 2009), or

* Corresponding author at: Department of Psychiatry and Psychotherapy, University Hospital Carl Gustav Carus, Technische Universität Dresden, 01307 Dresden, Germany.
Tel.: +49 351 4584474; fax: +49 351 4585316.
*E-mail address:* markus.donix@uniklinikum-dresden.de (M. Donix).
[1] Equal contributions.

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connectivity (Brown et al., 2011) which allow for the in vivo characterization of persons at risk for Alzheimer's disease. With its high resolution, MRI technology can provide the most direct in vivo visualization of neuronal structure in the various disease stages as reflected by the spatial patterns of gray matter atrophy (Thompson et al., 2003).

Neuropathological stages of the disease, first defined using histopathological methods and now visualized in the living brain using MRI, became essential for our understanding of Alzheimer's disease. Hemispheric differences in either direct or indirect measures of pathology are less well recognized. There is also no specific recommendation for how to address a possible hemispheric pathology distribution asymmetry in the original staging procedures (Braak and Braak, 1991). Without a clearer understanding of brain asymmetry differences in both pre-clinical and clinical Alzheimer's disease, it may be difficult, if not impossible, for clinicians to interpret such regional observations in individual subjects as disease-related or as a variant in brain development and aging.

Structural brain asymmetry and functional hemispheric specialization are fundamental features across species (Toga and Thompson, 2003). In the human brain, the perisylvian region shows the most prominent hemispheric asymmetry reflecting language specialization and handedness, which are interrelated in complex ways (Geschwind and Levitsky, 1968; Galaburda et al., 1978). Environmental and genetic factors contribute to the functional lateralization as well as to structural hemispheric asymmetry, ranging from gender and hormonal influences to experience-induced effects (Galaburda and Geschwind, 1981; Diamond, 1991; Diaz et al., 1994; Shaywitz et al., 1995). Pathological processes can also modulate hemispheric asymmetry and vice versa. Examples are planum temporale asymmetry reductions in dyslexia patients or gender-associated structural hemispheric asymmetry that possibly influences learning disorder incidence rate differences among men and women (Larsen et al., 1990; Toga and Thompson, 2003).

The hippocampus is a brain area for which hemispheric asymmetry has been reported in healthy individuals. In a meta-analysis, Pedraza et al. (2004) revealed larger right hippocampal volumes when compared with the left side in a sample of 82 studies. In a recent investigation, Lucarelli et al. (2013) also showed larger right hippocampal volumes in healthy adults. The authors detected a hemispheric asymmetry increase with age as well as gender effects with men showing greater asymmetry in hippocampus volumes (Lucarelli et al., 2013). Woolard and Heckers (2012) highlight that the functional relevance of this well-established right > left hippocampal volume asymmetry in healthy people is not well understood. However, regional asymmetry differences within the hippocampus as well as their differential predictive value for cognitive abilities, suggest a functional implication of this asymmetry (Woolard and Heckers, 2012).

Data also indicate that the left hemisphere could be more susceptible to neurodegeneration in Alzheimer's disease than the right hemisphere (Loewenstein et al., 1989; Janke et al., 2001). Although the spatial pattern of neuropathological changes in Alzheimer's disease development is relatively similar in both hemispheres, left hemispheric changes are more severe and may precede changes in the right hemisphere by up to 2 years (Thompson et al., 2003). This asymmetry in pathology distribution has been shown in vivo in patients with Alzheimer's disease, using metabolic measures, such as 18-F-fluorodeoxyglucose (FDG)-PET (Loewenstein et al., 1989) or advanced MRI based brain mapping techniques (Thompson et al., 2003). Histopathological data also show hemispheric asymmetry in neurofibrillary tangle but not amyloid plaque pathology distribution among postmortem samples from patients with Alzheimer's disease (Moossy et al., 1988). The neurofibrillary tangle asymmetry occurred in the hippocampus and entorhinal cortex but not in other brain regions investigated (Moossy et al., 1988). More recent histopathological data highlight that hemispheric asymmetry in Alzheimer's disease pathology distribution could even reflect different disease stages in the same brain (Stefanits et al., 2012). However, there is some variability in the existing literature. Postmortem histopathological findings did not suggest hemispheric differences (Arnold et al., 1991), and recent structural MRI data highlight asymmetric but not necessarily left-lateralized gray matter atrophy in Alzheimer's disease patients (Derflinger et al., 2011). It seems possible that patient groups differ in the pattern of contributing factors, such as disease severity or the presence of genetic variables, which could potentially influence hemispheric asymmetry.

Interestingly, the e4 allele of the apolipoprotein E gene (APOE-4), a major genetic risk factor for late-onset sporadic Alzheimer's disease (Corder et al., 1993) could be one of these variables. APOE-4 contributes to changes in brain structure and function already in children (Shaw et al., 2007) and young adults (Reiman et al., 2004). Data suggest that these changes do not reflect pathology but demonstrate the involvement of APOE proteins in brain development that influences physiological and pathological processes later in life. Such changes may render subjects at higher risk for Alzheimer's disease (Shaw et al., 2007), but the APOE-4 allele is also associated with improved cognitive abilities in childhood (Mondadori et al., 2007) and protective effects during embryogenesis (Zetterberg et al., 2002). These antagonistically pleiotropic APOE-4 characteristics at different stages of the life span are increasingly recognized in Alzheimer's disease research because of the shift towards younger study subjects driven by today's early detection focus.

In contrast, the possible influence of the APOE-4 allele on hemispheric differences in brain structure and function is less well investigated, although APOE effects are known to be regionally specific (Burggren et al., 2008; Donix et al., 2010a; Liu et al., 2010a). The evidence from childhood studies supports the existence of APOE-associated effects on asymmetric brain development. Using a voxel-based morphometric approach, Shaw et al. (2007) showed thinner entorhinal cortex in children and adolescents carrying the APOE-4 allele in the left hemisphere, whereas right entorhinal cortex thickness did not vary due to the risk allele. Children carrying the APOE-2 allele, which may have neuroprotective effects in late life (Talbot et al., 1994), showed reduced visuospatial skills and a higher prevalence of left-handedness than non-carriers of the allele (Bloss et al., 2010), again suggesting clinically relevant APOE effects on hemispheric asymmetry. In patients with Alzheimer's disease, Pievani et al. (2011) found smaller hippocampal volume in the left hemisphere but not in the right hemisphere among APOE-4 allele carriers when compared with non-carriers and healthy controls. Using FDG-PET, Alzheimer's disease patients carrying the risk allele compared with non-carriers showed differences in glucose metabolism in the left inferior temporal region only in a mild stage of the disease, suggesting APOE-4 involvement in the development rather than in the progression of the disease (Lee et al., 2003). It is in line with this hypothesis that other imaging studies did not find an association between the APOE-4 allele and hemispheric asymmetry in Alzheimer's disease (Hirono et al., 1998; Barnes et al., 2005), possibly indicating APOE-4 effects becoming less obvious with greater disease associated neural changes.

In this study we wanted to investigate whether carrying the APOE-4 allele would influence regional hemispheric asymmetry in patients with early Alzheimer's disease as well as in healthy middle-aged and older people. Using high resolution structural MRI and a cortical unfolding technique (Zeineh et al., 2001) we focused on the entorhinal cortex and the hippocampus. These regions are preferentially susceptible to Alzheimer's disease

**Table 1**
Demographic and clinical characteristics.

| Characteristic, mean ± S.D. | Healthy middle-aged | Healthy older | Alzheimer's disease |
|---|---|---|---|
| APOE carriers (no.) | 11 | 13 | 16 |
| APOE non-carriers (no.) | 15 | 10 | 12 |
| Age APOE-4 carriers (years, range) | 55.0 ± 8.4, 38–63 | 72.9 ± 6.4, 65–78 | 72.0 ± 4.9, 62–82 |
| Age APOE-4 non-carriers (years, range) | 55.6 ± 5.1, 46–63 | 68.0 ± 3.9, 66–86 | 72.6 ± 5.1, 65–74 |
| Female sex APOE-4 carriers (no.) | 7 | 6 | 8 |
| Female sex APOE-4 non-carriers (no.) | 13 | 6 | 5 |
| APOE-2/3 (no.) | 1 | 1 | 0 |
| APOE-3/3 (no.) | 14 | 9 | 12 |
| APOE-3/4 (no.) | 10 | 13 | 11 |
| APOE-4/4 (no.) | 1 | 0 | 5 |
| Positive family history (no.) | 12 | 13 | 10 |
| Education (years) | 16.0 ± 2.2 | 16.9 ± 3.2 | 14.4 ± 2.6 |
| MMSE (range 0–30) | 29.4 ± 0.9 | 29.0 ± 0.8 | 22.6 ± 4.0 |
| **Memory** | | | |
| WMS-III total VP (0–32) | 25.1 ± 5.4 | 21.8 ± 7.0 | |
| WMS-III delay total LM (0–50) | 31.7 ± 6.3 | 24.4 ± 8.2 | |
| CLTR (0–144) | 73.6 ± 32.1 | 53.4 ± 33.1 | |
| ROF delay (0–36) | 16.8 ± 4.9 | 14.2 ± 6.6 | |
| WMS-R VM DELAY (0–41) | | | 5.6 ± 5.7 |
| CERAD word list learning (0–30) | | | 12.3 ± 4.2 |
| CERAD word list recall (0–10) | | | 2.1 ± 1.5 |
| **Language** | | | |
| Boston naming test (0–60) | 55.8 ± 5.4 | 56.9 ± 2.7 | |
| FAS (no.) | 44.2 ± 12.6 | 40.9 ± 11.4 | |
| CERAD verbal fluency (no.) | | | 17.2 ± 4.5 |
| AAT single nouns (0–30) | | | 28.0 ± 1.3 |
| AAT composite nouns (0–30) | | | 27.6 ± 2.1 |
| **Attention, executive functioning** | | | |
| WAIS-III, digit span forward (no.) | 7.3 ± 1.2 | 6.8 ± 1.7 | |
| WAIS-III, digit span reverse (no.) | 5.2 ± 1.2 | 5.2 ± 1.7 | |
| Stroop interference (s) | 111.3 ± 21.7 | 123.4 ± 20.5 | |
| WCST total errors (no.) | 16.9 ± 9.3 | 24.4 ± 15.0 | |
| Trail making test, B (s) | 67.5 ± 22.9 | 75.7 ± 39.2 | 241.6 ± 70.5 |
| NAI labyrinth (s) | | | 95.6 ± 74.1 |
| **Visuospatial performance** | | | |
| ROF copy (0–36) | 29.9 ± 4.0 | 28.4 ± 4.6 | |
| WMS-R VM, copy (0–41) | | | 22.8 ± 7.5 |
| Trail making test, A (s) | | | 69.3 ± 37.8 |

MMSE—Mini Mental State Examination; WMS-III delay total LM—Wechsler memory scale, logical memory, delayed recall portion; WMS-III total VP—Wechsler memory scale, verbal paired associations II; ROF copy/delay—Rey Osterrieth Complex Figure, copy/delayed recall; WAIS-III—Wechsler Adult Intelligence Scale; FAS—Controlled oral word association test, letters F, A, S; CLTR—Buschke–Fuld selective reminding test, consistent long-term retrieval section; WCST—Wisconsin card sorting test; CVLT—California Verbal Learning Test; WMS-R VM—Wechsler Memory Scale Revised, Visual Memory, CERAD—Consortium to Establish a Registry for Alzheimer's Disease; AAT—Aachen Aphasia Test; and NAI—Nuremberg age inventory.

pathology (Braak and Braak, 1991), and they exhibit APOE-associated structural changes detectable with MRI in healthy people across the life span (Shaw et al., 2007; Burggren et al., 2008; Donix et al., 2010b). We hypothesized that healthy APOE-4 carriers compared with non-carriers show a greater left-right hemispheric asymmetry in entorhinal and hippocampal cortical thickness, whereas the risk allele's influence would be less substantial in patients with Alzheimer's disease.

## 2. Methods

### 2.1. Subjects

Seventy-seven subjects participated in this study (Table 1). We took advantage of an international collaboration to compare Alzheimer's disease patients ($N$=28, mean age 72.0 ± 4.9 years) with middle-aged ($N$=26, mean age 55.3 ± 6.6 years) and older ($N$=23, mean age 71.4 years ± 6.2 years) cognitively healthy subjects from our prior work (Donix et al., 2010a). Healthy participants were recruited through advertisements at the UCLA Semel Institute for Neuroscience and Human Behavior in Los Angeles, USA. Alzheimer's disease patients were recruited for a longitudinal study investigating biological and clinical parameters (baseline data are used in the present study) at the university hospital's memory clinic of the Technische Universität Dresden, Germany. After complete description of the study to the subjects, written informed consent was obtained in accordance with the UCLA Human Subjects Protection Committee (healthy participants), and in accordance with Dresden University's Ethics Committee (Alzheimer's disease patients). We only recruited Alzheimer's disease patients with early-stage disease (CDR stage 1) who had the full capacity to consent. This was established in a clinical evaluation by an independent psychiatrist.

Although recruited and scanned at different locations, our aim was not to compare these subject groups directly in the statistical methods detailed below. All subjects underwent APOE genotyping, MRI scanning, and neuropsychological assessments. Cognitive status was assessed with standardized tests for several cognitive domains, such as memory, language, attention/executive functioning, and visuospatial skills. Our subjects did not have a history of psychiatric or neurological disorder (except Alzheimer's disease in the patient group) or a major systemic disease affecting brain function. Alzheimer's disease patients showed cognitive impairments according to standard clinical criteria (McKhann et al., 1984). Healthy younger and older participants performed within the age norms in all neuropsychological tests. Alzheimer's disease diagnosis was established by a geriatric psychiatrist, based on a clinical evaluation and neuropsychological examination results. Structural MRI evaluation and laboratory testing complemented the diagnostic procedures to rule out conditions that would have explained the dementia syndrome otherwise. All but one healthy subject carrying the APOE-4 allele were heterozygous APOE 3/4 allele carriers; five of the APOE-4 positive Alzheimer's disease patients were homozygous for the variant. Two healthy subjects were APOE 2/3 carriers, all other non-carriers in the healthy participant and patient groups

were homozygous APOE 3/3 carriers. There were no APOE 2/4 or APOE 2/2 carriers among study participants. Only right-handed subjects participated in this study; we excluded two left-handed individuals from our healthy subject groups. Alzheimer's disease patients were on stable ( > 6 weeks) acetylcholinesterase inhibitor medication, and all patients and healthy participants did not receive any other medication that could influence cognitive functioning. Investigators performing scanning and cortical unfolding procedures were unaware of the participants' clinical and demographic information, such as APOE status. They also did not know that the study hypotheses were related to hemispheric asymmetry.

### 2.2. Procedures

MRI scanning was performed on a Siemens Allegra 3-Tesla MRI scanner (Siemens Medical Solutions, Inc., Malvern, Pa) for all healthy subjects and on a GE Signa HDxt 3-Tesla scanner (General Electric Health Care, Waukesha, Wisconsin) for Alzheimer's disease patients. We acquired high-resolution oblique coronal T2-weighted fast-spin echo sequences for cortical unfolding (repetition time: 5200 ms; echo time: 105 ms; slice thickness: 3 mm; spacing: 0 mm; 19 slices; in-plane voxel size: $0.39 \times 0.39$ mm$^2$; and field of view: 200 mm). The cortical unfolding method improves the visibility of the convoluted medial temporal lobe cortex by flattening the entire gray matter volume into two-dimensional space (Zeineh et al., 2001, 2003). First, gray matter is specified by manually masking non-gray matter regions on oblique coronal fast-spin echo MRI data. Because of the greater anatomical variability in-plane when compared with the variability along the long axis of the hippocampus, slice thickness was initially sacrificed to maximize in-plane resolution. To improve segmentation, the original images are therefore interpolated by a factor of seven, resulting in an approximately isotropic voxel size. After segmentation, using a region-expansion algorithm, gray matter is grown out in connected layers resulting in a gray-matter volume containing cornu ammonis (CA) fields 1–3, the dentate gyrus, the subiculum, entorhinal, perirhinal, and parahippocampal cortices, and the fusiform gyrus. Boundaries between these subregions are defined on the original in-plane MRI images (Fig. 1), based on histological and MRI atlases (Amaral and Insausti, 1990; Duvernoy, 1998), and mathematically projected to their flat map space coordinates. For cortical thickness calculations, each gray matter voxel's distance to the nearest non-gray matter voxel is first computed in 3D space. In 2D space, for each flattened voxel representation, the maximum distance value of the corresponding 3D voxels across all layers is taken and multiplied by two. Hippocampal thickness was computed by averaging across hippocampal subregions (cornu ammonis fields and dentate gyrus). The topographical accuracy of the unfolding technique has been demonstrated extensively, including reconstruction of the hippocampus from a flat map (Zeineh et al., 2001, 2003; Burggren et al., 2008; Ekstrom et al., 2009; Donix et al., 2010a, 2010b). Intra-rater reliability (intra-class correlation coefficient [ICC] range 0.969–0.994 across subregions, Burggren et al., 2008), and test–retest reliability (test–retest cortical thickness measurement differences 0.1–1.2% across subregions, Donix et al., 2010b) analyses have been reported as well.

We report raw cortical thickness data, which is in line with our previous work (Burggren et al., 2008; Donix et al., 2010a, 2010b). It also reflects an image analysis strategy that should be applied to cortical thickness measurements in contrast to volumetric data (Westman et al., 2013). Using paired Wilcoxon signed rank tests we determined the significance of right–left hemispheric cortical thickness differences among carriers and non-carriers of the APOE-4 allele in each group. In order to control for age in a nonparametric setting, we conducted an ANCOVA using the ranks of the left–right cortical thickness differences as the dependent variable, and the ranks of the ages as the covariate. Although we were primarily interested in the hippocampal and entorhinal regions, we used a Bonferroni corrected threshold of $p < 0.007$ in order to minimize spurious findings within the seven medial temporal lobe regions that can be separated in the MRI analyses.

## 3. Results

Healthy participants carrying the APOE-4 allele when compared with healthy subjects without this risk factor showed a significant thinner entorhinal cortex in the left hemisphere (approximately 10%) when compared with the right hemisphere

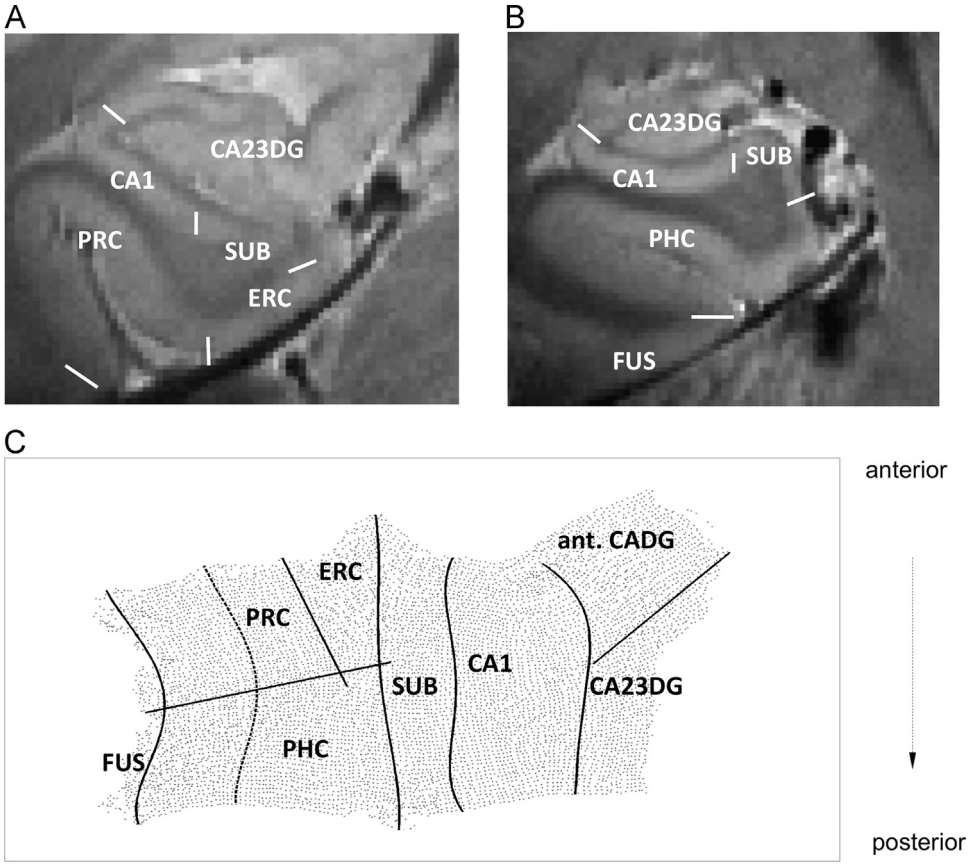


**Fig. 1.** Cortical unfolding. After manual segmentation of white matter and cerebrospinal fluid on high-resolution magnetic resonance images the resulting gray matter is computationally unfolded and flattened [C, right side shown]. Boundaries between subregions are delineated on all images acquired covering the hippocampal region from anterior [A] to posterior [B] parts. These demarcations are later projected onto the two-dimensional map. CADG = anterior cornu ammonis fields and dentate gyrus, CA23DG = cornu ammonis fields 2,3 and dentate gyrus, CA1 = CA field 1, SUB = subiculum, ERC = entorhinal cortex, PRC = perirhinal cortex, PHC = parahippocampal cortex, and FUS = fusiform cortex (boundary depicts medial fusiform vertex).

(healthy middle-aged participants: left hemisphere 11.3% thinner, $p=0.002$, Cohen's $d=1.12$; healthy older participants: 10.2%, $p=0.004$, $d=0.8$). In contrast, among healthy non-carriers of the risk allele the difference between the left and right entorhinal cortex thickness (approximately 5% thinner left hemisphere) was not significant at the predefined statistical threshold (healthy middle-aged: 4.8%, $p=0.09$, $d=0.35$; healthy older participants: 6.3%, $p=0.07$, $d=0.67$). Among Alzheimer's disease patients, both APOE-4 carriers (9.7%, $p<0.001$, $d=0.85$) as well as non-carriers of the APOE-4 allele (11.3%, $p=0.004$, $d=1.45$) showed this entorhinal cortex asymmetry. Cortical thickness in the hippocampus and other medial temporal lobe regions (perirhinal, and parahippocampal cortices, and the fusiform gyrus) did not vary between hemispheres due to the APOE-4 allele (Fig. 2). In the hippocampus, the non-significant differences between left and right hemispheric cortical thickness ranged from 2.1% thinner left hemisphere ($p=0.2$, $d=0.24$) among older healthy APOE-4 carriers to 1.5% thinner right hemisphere ($p=0.4$, $d=0.16$) among Alzheimer's disease patients also carrying the risk allele. All other subgroups' results for the hippocampus did not exceed these maxima.

The age distribution within each group did not influence the pattern of significant results. We also did not find a correlation (using Pearson's correlations) between neuropsychological test performance and cortical thickness measurements. We examined possible associations between cortical thickness and neuropsychological test performance in all subregions, within each side as well as using a right–left asymmetry score. None of these associations yielded a significant finding. In this study neuropsychological tests are only provided for subject sample characterization. It was not the focus of this study to primarily investigate associations between neuropsychological test results and cortical thickness. Therefore these correlation analyses were exploratory and we did not perform further analyses of covariance to evaluate the influence of other parameters, such as age, on these associations.

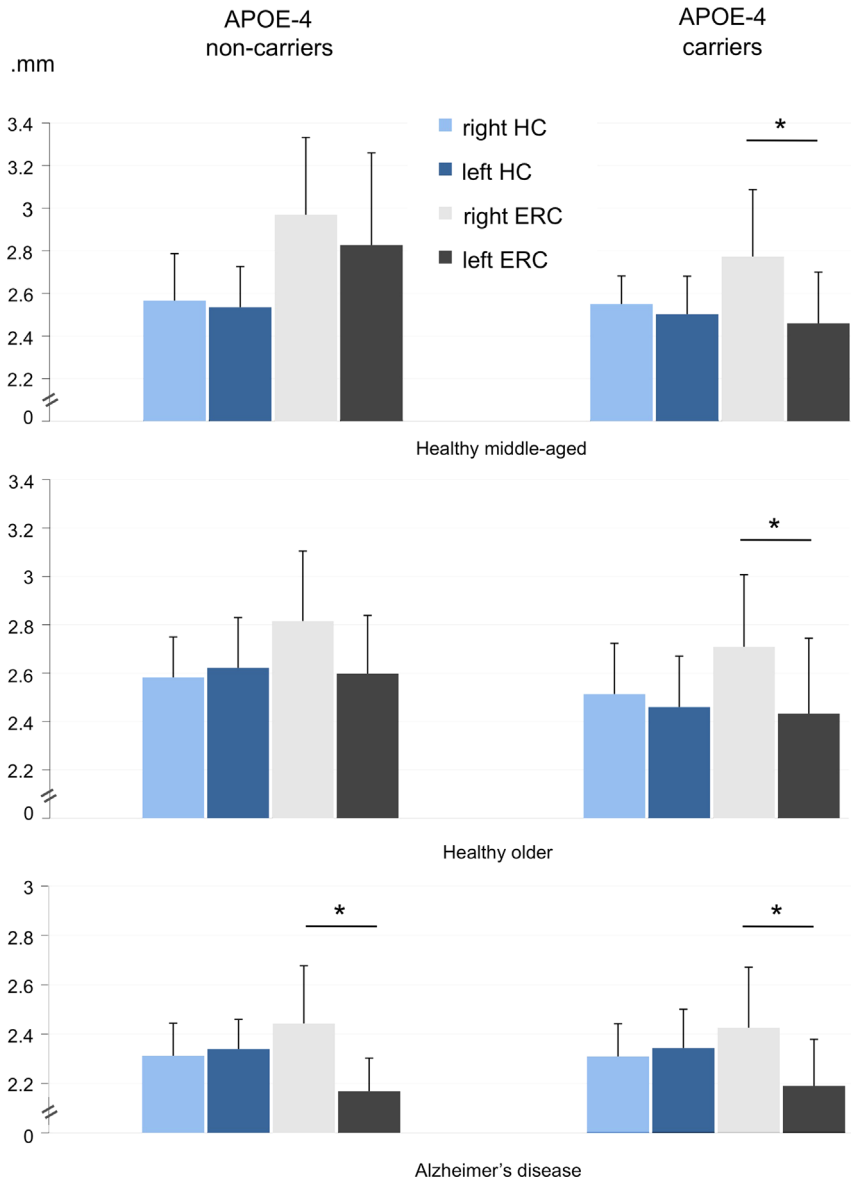


**Fig. 2.** Hemispheric cortical thickness asymmetry in the hippocampus and entorhinal cortex. Apolipoprotein E e4 allele carriers show a left–right cortical thickness asymmetry in the entorhinal region (ERC) among all study participants, whereas non-carriers of the risk allele show this regional asymmetry only in the Alzheimer's disease patient group. In the hippocampus (HC), hemispheric cortical thickness differences do not vary due to the presence of the APOE-4 allele. Raw means, error bars represent standard deviation. Significant differences are indicated (*$p<0.007$, Bonferroni corrected).

## 4. Discussion

Our data reveal an APOE-4 allele associated hemispheric cortical thickness asymmetry in the entorhinal region. Carriers of the risk allele show thinner entorhinal cortex in the left hemisphere when compared with the right hemisphere, irrespective of age or cognitive abilities. Non-carriers diagnosed with Alzheimer's disease also show this regional cortical thickness asymmetry. First we want to highlight that brain structure asymmetry detected in cross-sectional studies has to be interpreted with caution, since the possible underlying dynamics, such as loss of tissue, can only be determined in longitudinal assessments.

Innovative brain mapping techniques suggest a left-lateralized hemispheric asymmetry in Alzheimer's disease development (Thompson et al., 2003, 2007). However, it remains largely unknown why this asymmetry exists, and whether it interacts with functional hemispheric specializations, such as handedness or language predominance. It is also unclear, whether asymmetrical brain structure changes in aging and Alzheimer's disease mirror an unequal burden of regional neuropathology or perhaps additional developmental hemispheric differences in neuronal architecture that may influence atrophy patterns.

It is likely that in this highly heritable disease (Gatz et al., 2006) genetic factors largely contribute to characteristics in brain structure. This raises the interesting question how risk alleles, such as APOE-4, exactly mediate Alzheimer's disease risk. For the APOE-4 allele there is evidence for various possible mechanisms, associated with changes in lipid metabolism, insufficient neuronal plasticity, increased amyloid plaque production and tau tangle phosphorylation, or even direct neurotoxicity (Saunders, 2000; Teter, 2004; Mahley et al., 2006). On the molecular level these processes are often intuitively perceived as 'pathologic' or 'dysfunctional'. However, neuroimaging findings from childhood and adolescence data also suggest the APOE-4 allele's involvement in normal brain development (Zetterberg et al., 2002; Mondadori et al., 2007; Shaw et al., 2007). APOE-4 associated features, such as thinner entorhinal cortex (Shaw et al., 2007), may not themselves reflect pathology but they could possibly contribute to future patterns of spatial and temporal pathology distribution. Hemispheric differences in neuronal structure could be a disadvantage in case a neurodegenerative disease occurs later in life, resulting in lateralized distribution of pathological changes due to earlier structural and functional impact of pathology in the smaller region. Higher aging-related atrophy rates in the entorhinal and hippocampal region among cognitively healthy APOE-4 carriers also suggest that the risk allele's effects on brain structure are more dynamic with increasing age (Thompson et al., 2007; Donix et al., 2010b). These findings and our data presented here illustrate how high-resolution MRI data influence our understanding of APOE-4 associated risk mechanisms. The association of the risk variant with hemispheric differences in entorhinal cortical thickness could contribute to pathology asymmetry towards the left hemisphere in early Alzheimer's disease (Thompson et al., 2003, 2007), and therefore to the characteristic clinical changes in the patients' cognitive abilities.

We did not detect hemispheric asymmetries in the hippocampus or other medial temporal lobe subregions, such as the perirhinal and parahippocampal cortices, and the fusiform gyrus. This also emphasizes the unique role of the entorhinal cortex in Alzheimer's disease-related pathology. However, hippocampal hemispheric asymmetry has been demonstrated previously among healthy adults (Pedraza et al., 2004; Lucarelli et al., 2013). A major difference between our data and these studies is that we measure cortical thickness instead of volume. It is difficult to directly compare volume and thickness data. Volume reduction in medial temporal regions, specifically among older healthy adults, may occur because of reduced cortical surface area rather than cortical thinning (Dickerson et al., 2009). Furthermore, automated segmentation methods used for large-scale volumetric studies of the hippocampus may provide the best results in younger healthy adults, whereas hippocampal shape deformation processes in aging and dementia make registration to standard brain atlases challenging. Hippocampal volumetry with standard brain segmentation tools may comprise functionally distinct subregions that could be separated using manual tracing. Our cortical thickness data as well as previous volumetric results (Woolard and Heckers, 2012) show that the medial temporal region including the hippocampus should not be perceived as a homogeneous area with respect to hemispheric asymmetry. It is also possible that hemispheric asymmetry is mediated by other factors in addition to the APOE genotype. Existing studies on hemispheric asymmetry may not often focus on (e.g., genetic) covariates, and how they interact with asymmetry in aging and disease.

Non-carriers of the risk allele diagnosed with Alzheimer's disease also show hemispheric asymmetry in entorhinal cortical thickness. This indicates the existence of other, disease-related mechanisms contributing to regional brain asymmetry changes. It would be in line with the hypothesis of APOE-4 being more important for disease development than for disease progression (Lee et al., 2003). However, in a longitudinal analysis, Thompson et al. (2011) showed that subtle APOE-4 associated changes in entorhinal cortical thickness trajectories are detectable among Alzheimer's disease patients.

Insufficient information about APOE allele distribution in a given population could also be one of the explanations for imaging data variability among studies investigating hemispheric asymmetry in aging and Alzheimer's disease. The interaction with gender and age, and disease severity could further influence APOE-associated findings (Qiu et al., 2004). Raz et al. (2004) found accelerated volume loss in the entorhinal cortex and the hippocampus with increasing age in healthy individuals. However, risk factor associated differences in cortical thickness or volume in a specific brain area do not sufficiently explain a region's susceptibility to Alzheimer's disease pathology. Recent fMRI data show altered medial temporal lobe connectivity with the posterior cingulate cortex among young APOE-4 carriers (Dennis et al., 2010). PET findings indicate APOE-associated neuropathology burden differences in cognitively healthy individuals (Small et al., 2009). This highlights that complementary scientific methods are necessary to determine whether APOE-related morphologic features contribute to or are associated with changes in neural integrity that influence brain functioning. Future studies could also focus on other allelic APOE variants. The sample size of the current study was too small to investigate this. The existing literature is limited and variable findings have stimulated some debate. People carrying the APOE-2 allele are less likely to develop Alzheimer's disease pathology than non-carriers of this allele (Benjamin et al., 1994), and its 'protective' effects (Qiu et al., 2004) might be associated with brain structure characteristics in the entorhinal region and the medial temporal lobe (Shaw et al., 2007; Liu et al., 2010b). It remains controversial whether the APOE genotype contributes to differences in functional hemispheric specialization, such as handedness (Bloss et al., 2010; Piper et al., 2013), or whether there is an association of hemispheric specialization and vulnerability to Alzheimer's disease pathology (de Leon et al., 1986).

In addition to allelic APOE variants and their interaction with age and neural pathology distribution, gender-associated effects should also be considered. Qiu et al. (2004) showed a stronger APOE-4 associated risk effect in men when compared with women. Women, however, show higher Alzheimer's disease prevalence and incidence rates (Jorm et al., 1987; Rocca et al., 1991), although life expectancy differences could contribute to this

finding (Hebert et al., 2001). Whether this gender variance is mediated by different patterns of structural and functional hemispheric specialization during brain development, and whether these differences are influenced by the APOE genotype remain to be investigated. There is evidence for gender differences in right-hemispheric visuospatial task performance, and left-hemispheric linguistic tasks (Benbow and Stanley, 1983). Hormonal levels are believed to modulate underlying differences in brain structure and hemispheric asymmetry between men and women, which already develop in utero (Galaburda and Geschwind, 1981; Witelson, 1991).

This study has limitations that should be mentioned. First, the sample size is relatively small. Despite the robust APOE-4 associated finding in the entorhinal cortex across all participants, sample size could have influenced our ability to detect subtle asymmetry effects in our primary regions of interest. Furthermore, Alzheimer's disease pathology could already be present in some of the cognitively healthy individuals. Other risk factors, such as a first-degree family history of Alzheimer's disease could modulate brain structure (Donix et al., 2010a). Gender effects could additionally modify how risk factors influence brain asymmetry. However, our study was not primarily aimed at investigating these variables. Furthermore, whether or not there is an interaction of such variables with neuronal pathology, or whether or not this is reflected by changes in hemispheric asymmetry cannot be revealed using structural MRI alone. In order to examine brain structure changes in a continuum from normal cognitive aging to dementia, future studies should also include patients with mild cognitive impairment. This could provide additional insight into APOE effects at different stages of Alzheimer's disease development. We blinded investigators performing manual segmentation procedures of MRI data to demographic information and APOE genotype, but they were aware of analyzing the left or right hemisphere. Although this could be a potential confounder, these investigators did not know that the study hypotheses were related to hemispheric asymmetry, which should have minimized the effect. However, Maltbie et al. (2012) highlight that there could even be a bias towards a left–right hippocampal asymmetry caused by the rater's laterality of visual perception.

Alzheimer's disease patients and healthy subjects were scanned with different MRI scanners. Although gray and white matter contrast differences were comparable resulting in similarly accurate cortical thickness measures, Siemens and GE scanners may produce data that is slightly different, e.g., due to pulse sequence programming differences. This may result in slightly different estimates of thickness measures across scanners. However, only Alzheimer's disease patients were scanned with the GE scanner. Although we did not intend to compare cortical thickness of healthy subjects and Alzheimer's disease patients, possible cross-scanner measurement differences do not exceed disease associated cortical thinning effects (Han et al., 2006; Dickerson et al., 2009). Finally, our results should be confirmed in future studies using a larger subject sample. We utilized an innovative MRI analysis technique specifically aimed at investigating hippocampal and adjacent medial temporal substructures. Our semi-automated procedures involve manual segmentation of the area. In comparison with automated techniques, this approach yields superior results with respect to how many subregions can be distinguished, and provides the possibility of segmenting brains that do not show normal anatomy. Medial temporal lobe atrophy, for example, could interfere with automated segmentation procedures. Databases, such as ADNI, have the advantage of providing a large number of subjects, reducing statistical power issues, and analyses are not limited to the medial temporal lobe. Unfortunately, for our analysis approach, MRI scanning requirements range from a specific angle perpendicular to the long axis of the hippocampus to very high in-plane resolution, which cannot be obtained from ADNI or other comprehensive data resources.

In summary, our data reveal an association of the APOE-4 allele with left–right hemispheric asymmetry in entorhinal cortical thickness among all subject groups, while in Alzheimer's disease patients this asymmetry was also detectable among non-carriers of the risk allele. The APOE-4 genotype may contribute to hemispheric differences in the temporal pattern of early Alzheimer's disease pathology development. Together with the available childhood and adolescence data, our finding supports the existence of an age-independent APOE-4 effect on neuronal structure, which may interact with a neurodegenerative process later in life. This could increase the awareness for a less exclusively pathology-oriented interpretation of radiological brain anatomy features associated with a risk gene.

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