Relationship between APOE Genotype and Structural MRI Measures throughout Adulthood in the Study of Health in Pomerania Population-Based Cohort

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ABSTRACT

BACKGROUND AND PURPOSE: The presence of the apolipoprotein E e4 allele is the strongest sporadic Alzheimer disease genetic risk factor. We hypothesized that apolipoprotein E e4 carriers and noncarriers may already differ in imaging patterns in midlife. We therefore sought to identify the effect of apolipoprotein E genotype on brain atrophy across almost the entire adult age span by using advanced MR imaging–based pattern analysis.

MATERIALS AND METHODS: We analyzed MR imaging scans of 1472 participants from the Study of Health in Pomerania (22–90 years of age). We studied the association among age, apolipoprotein E e4 carrier status, and brain atrophy, which was quantified by using 2 MR imaging–based indices: Spatial Pattern of Atrophy for Recognition of Brain Aging (summarizing age-related brain atrophy) and Spatial Pattern of Abnormality for Recognition of Early Alzheimer Disease (summarizing Alzheimer disease-like brain atrophy patterns), as well as the gray matter volumes in several Alzheimer disease- and apolipoprotein E–related ROIs (lateral frontal, lateral temporal, medial frontal, and hippocampus).

RESULTS: No significant association was found between apolipoprotein E e4 carrier status and the studied ROIs or the MR imaging–based indices in linear regression models adjusted for age, sex, and education, including an interaction term between apolipoprotein E and age.

CONCLUSIONS: Our study indicates that measurable apolipoprotein E–related brain atrophy does not occur in early adulthood and midlife and suggests that such atrophy may only occur more proximal to the onset of clinical symptoms of dementia.

ABBREVIATIONS: AD = Alzheimer disease; APOE = apolipoprotein E; MCI = mild cognitive impairment; SHIP = Study of Health in Pomerania; SNP = single nucleotide polymorphism; SPARE-AD = Spatial Pattern of Abnormality for Recognition of Early Alzheimer Disease; SPARE-BA = Spatial Pattern of Atrophy for Recognition of Brain Aging.

The presence of the apolipoprotein E gene (APOE) e4 allele is the strongest genetic sporadic Alzheimer disease (AD) risk factor. The APOE gene has 2 additional codominant alleles (APOE e2 and e3). These alleles code for the 3 corresponding apolipoprotein isoforms (ApoE e2, e3, and e4). Compared with individuals with the e3 allele, which is the most common in the general population, those with the APOE e4 allele have a higher risk of AD, whereas the APOE e2 allele is associated with a lower risk of AD. The APOE genotype modifies the age at which cognitively healthy subjects present biomarker changes that define AD preclinical stages. There are several mechanisms that have been of data; S.M.R.: analysis and interpretation of data; J.D.: analysis and interpretation of data; S.V.d.A.: acquisition of data; G.E.: analysis and interpretation of data; D.J.: acquisition of data; K.H.: acquisition of data; G.H.: acquisition of data; H.V.: acquisition of data, analysis and interpretation of data; W.H.: acquisition of data, analysis and interpretation of data; and H.J.G. and C.D.: conception and design, acquisition of data, and analysis and interpretation of data. Please address correspondence to Mohamad Habes, PhD, Center for Biomedical Image Computing and Analytics, University of Pennsylvania, 3700 Hamilton Walk, Philadelphia, PA 19104; e-mail: habesm@uphs.upenn.edu; Jon B. Toledo, MD, Department of Pathology and Laboratory Medicine, Institute on Aging, Center for Neurodegenerative Disease Research, University of Pennsylvania Perelman School of Medicine, Philadelphia, Pennsylvania; Laboratory of Behavioral Neuroscience (S.M.R), University of Pennsylvania, Philadelphia, Pennsylvania; Center for Biomedical Image Computing and Analytics, University of Pennsylvania, 3700 Hamilton Walk, Philadelphia, PA 19104; e-mail: jtoledo@mail.med.upenn.edu. Indicates article with supplemental on-line appendix and tables. Indicates article with supplemental on-line photos.
associated with the influence of APOE e4 on AD risk: decreased clearance of amyloid from the brain, impaired synaptic plasticity, altered blood-brain barrier permeability, and immune response and impaired membrane repair following neuronal injury. In line with these results, neuropathologic studies have shown that plaques and tangles mediate APOE-related clinical changes. ApoE is present in plasma and CSF, but there is a weak correlation between ApoE concentrations within these 2 compartments. In APOE genotype–adjusted models, CSF, but not plasma, ApoE levels are associated with cognitive changes and brain atrophy. Nevertheless, a large longitudinal study reported associations with plasma ApoE levels that dropped to borderline significance when adjusted for the APOE genotype.

Most APOE-related findings regarding brain structure have been reported in elderly subjects. However, due to the long AD preclinical stage, it could be expected that subtle neuroimaging changes may appear at younger ages and become more pronounced with advancing age. In line with this hypothesis, there is limited information regarding associations related to brain structural changes and APOE genotypes in younger subjects. Previous studies have reported lower hippocampal, orbitofrontal, and entorhinal volumes in subjects with APOE e4 in the first decades of life. Other studies have shown brain hypometabolism in AD-related areas and increased activation of the default mode network in young APOE e4 carriers but no differences in gray matter volume. The aforementioned changes reported in these studies would be taking place during the 3 decades before the ages that show at least 1% AD prevalence. These findings suggest that AD could have a neurodevelopmental component. However, the relation between regional brain atrophy and the APOE genotype needs to be evaluated across the adult life span.

We hypothesized that APOE e4 carriers and noncarriers could present different imaging patterns that start differing in midlife, much earlier than clinical diagnosis. To investigate this hypothesis, we sought to model structural MR imaging brain changes associated with the APOE genotype in a large population-based study spanning the third-to-ninth decades of life by using sensitive pattern-based aging and AD summary indices.

**MATERIALS AND METHODS**

**Participants from the Study of Health in Pomerania**

The Study of Health in Pomerania (SHIP) is a prospective cohort whose subjects are recruited from the general population of the German State of Mecklenburg–Western Pomerania. It is led by the Institute for Community Medicine at the Medical Faculty of the University of Greifswald. SHIP started at baseline with SHIP-0 between 1997 and 2001. After about 5 years, all participants were reinvited for a follow-up visit (ie, SHIP-1). From 2008 to 2012, the second follow-up examination, SHIP-2, was performed. Concurrent with SHIP-2, a new population sample from the same area was drawn, and similar examinations were undertaken between 2008 and 2012 (SHIP-TREND).

**Table 1: Description of the SHIP sample included in this study (n = 1472)**

| Characteristic                          | SHIP-2 | SHIP-TREND | SHIP-2 and SHIP-TREND (Analysis Sample) |
|----------------------------------------|--------|------------|----------------------------------------|
| Age (median) (SD) [yr]                 | 56.3 (12.2) | 51.3 (13.4)* | 53.3 (13.0) |
| Education (No.) (%)                    | 137 (8.4) | 77 (10.6)* | 214 (14.5) |
| <8 yr                                  | 430 (57.8) | 415 (57.0)* | 845 (57.4) |
| 8–10 yr                                | 177 (23.8) | 236 (32.4)* | 413 (28.1) |
| 10 yr                                  | 145 (19.5) | 177 (24.3)* | 322 (21.9) |
| APOE genotype: at least 1 e4 allele (No.) (% positive) | 399 (53.6) | 421 (57.8) | 820 (55.7) |
| Female sex (No.) (%)                   | 8.6 (3.0) | 11.2 (2.5) | |
| Verbal Learning and Memory Test (mean) (SD) | | | |
| Nuremberg Age Inventory (mean) (SD)    | | | |

* Significant difference at P < 0.05.
1 × 1 mm in-plane spatial resolution, section thickness = 1.0 mm, flip angle = 15°, TE = 3.4 ms, TR = 1900 ms.

**Image Processing**
An automated multiaxis segmentation method was applied on the T1-weighted image of each subject to calculate a brain mask, by removing extracranial material on the T1-weighted image.20 Total intracranial volume was estimated by calculating the volume of a subject’s brain mask, which included the volumes of gray matter, white matter, ventricles, and the CSF that were contained within the outer brain boundary. Each brain mask was visually inspected for quality, by M.H., and all low-quality brain masks (including either under- or oversegmented brain) were excluded.

A multiaxis label fusion–based segmentation method21 was applied for segmentation of the brain into a set of anatomic ROIs. The volumes of ROIs were calculated and were normalized by total intracranial volume. In this analysis, we selected a set of gray matter ROIs on the basis of areas that were associated with AD-related atrophy and previously reported APOE-related findings. Further details are given in the On-line Appendix (On-line Method 1).

**MR Imaging Pattern Classification**
A pattern-classification method was previously proposed to derive Spatial Pattern of Abnormality for Recognition of Early AD (SPARE-AD),22 an index summarizing the high-dimensional imaging data with a single value that quantifies the atrophy patterns in AD-related regions. SPARE-AD has been shown to discriminate between normal cognition and mild cognitive impairment (MCI)23 and conversion from MCI to AD.24 We calculated, in this study, the SPARE-AD index for the SHIP population by using a model based on a linear support vector machine,25 which was trained on the external training dataset described in Da et al24 and had been validated earlier.26 More positive SPARE-AD implies a more Alzheimer disease–like brain structure, while more negative values reflect more normal brain structure.

Similar to the calculation of the SPARE-AD index, a linear support vector machine–based model was designed to predict an individual’s age from the MR image and was used for quantifying Brain Aging (BA), summarized by the SPARE-BA index.22 The classification model was trained for optimally discriminating young and old subject groups and has been recently described.26,27 The SPARE-BA index for an individual implied fewer brain aging patterns for higher (positive) values and the presence of more aging-related atrophy patterns for lower (negative) values. While the SPARE-AD index captured more localized atrophy patterns in AD-related regions, such as in the hippocampus and temporal lobe, the SPARE-BA index captured more global aging patterns, distributed in the cortex, but particularly in the frontal lobe. Further details are given in the On-line Appendix (On-line Method 2).

**APOE Determination in SHIP**
The APOE genotypes were determined on the basis of rs429358(C;C) and rs7412(T;T) from the resulting imputation of the SHIP genotyping. More details can be found in the On-line Appendix (On-line Method 3).

**Statistical Analysis**
We studied the association between age, the APOE e4 genotype, and AD-related gray matter volume (lateral frontal, lateral temporal, medial frontal, and hippocampus), as well as SPARE-AD and SPARE-BA, for the 1472 SHIP participants included in this study. In this study, subjects with at least 1 e4 allele were considered to have the APOE e4 genotype.

We applied linear regression models, which included total intracranial volume normalized ROI volumes as outcomes, and age square (if significant), age, APOE e4 carrier status, and sex as predictors adjusting for education level and study cohort. We also investigated the significance of interaction terms between the APOE e4 status and the variables: age, age, education, and sex, after adding those interaction terms one at a time to the regression models as predictors. Results were considered statistically significant if the 2-sided P value was <.05. No multiple comparison adjustment was applied because analyses were performed on a small number of predictors that were selected on the basis of previously published findings rather than determined on the basis of the data derived therein. To identify potentially cognitively impaired subjects on the basis of the residuals of linear regressions between age and the available cognitive scores, we labeled those subjects with a z-score of less than −1.5 SDs as possibly cognitively impaired (n = 98) (On-line Fig 1). Spearman rank correlation coefficients were used to assess correlations between variables. The Student t test was used to compare continuous variables, and the Pearson χ² test, to compare categoric variables. Analyses were performed by using the R statistical and computing software, Version 3.1 (http://www.r-project.org/).

**RESULTS**

**Subjects Included in the Study**
A total of 1472 participants, from which 744 belonged to SHIP-2 and 728 belonged to SHIP-TREND, with ages ranging from 22 to 90 years (median, 53.3 years), were included in the analyses. Cohorts did not differ in sex, but significant differences were present with respect to education level (P < .001), age (P < .0001), and the number of APOE e4 carriers (P = .03). No differences were seen between subjects included in the study and those who were excluded based on the inclusion criteria described in the “Materials and Methods” section, except for sex (On-line Table 1).

**Association between the MR Imaging–Based Indices and Age**
The Spearman rank correlation coefficient was r = 0.36 between age and SPARE-AD, and r = −0.77 between age and SPARE-BA (P < .001). The Spearman rank correlation coefficient between SPARE-AD and SPARE-BA was r = −0.44 (P < .001).

**Association between APOE and MR Imaging Findings**
Figure 1 shows the relationship between the AD-related gray matter regions and age in APOE e4 carrier and noncarrier individuals. Similarly, Fig 2 shows the relationship between the MR imaging–based indices and age. In the age- and sex-adjusted models that included the interaction term between APOE and age, no significant association was found between APOE e4 carrier status and the studied MR imaging measurements in the regression models that in-
cluded the ROI volumes or the SPARE indices as outcomes (Table 2). Similarly, there was no significant interaction between APOE e4 carrier status and age ($P > .1$). In all models, older age was associated with greater brain atrophy, and a nonlinear square age term was significant for the models that included the lateral temporal regions, hippocampus, or SPARE-AD scores as outcomes (Table 2). Besides age, male participants showed smaller regional volumes, higher SPARE-AD, and lower SPARE-BA values over the studied life span. In additional analyses limiting the sample to younger (22–40 years) or older (60–90 years) participants, we did not find any APOE genotype–related differences (On-line Tables 2 and 3).

**Association between APOE and Cognitive Scores**

No significant association was detected among the Verbal Learning and Memory Test, Nuremberg Age Inventory, and APOE e4 carrier status in a linear regression model after adjusting for age, sex, and education (On-line Tables 4 and 5).
Table 2: Linear regression models between age and ROI volumes (normalized by total intracranial volume) and SPARE-AD and SPARE-BA

| Outcome                      | Age         | Age² | Female       | APOE e4 Carriers |
|------------------------------|-------------|------|--------------|------------------|
| Lateral frontal volume       | −0.0003900  | <0.01| 0.0021720    | −0.0002459 (.433) |
| Lateral temporal volume      | 0.0001020   | <0.04| 0.0003695    | 0.0001112 (.605) |
| Medial frontal volume        | −0.0001291  | <0.01| 0.0001690    | −0.0000555 (.964) |
| Hippocampal volume           | 0.0000415   | <0.01| 0.0001919    | 0.0000118 (.649) |
| SPARE-AD                     | −0.0438960  | <0.01| −0.1775256   | 0.0293579 (.582) |
| SPARE-BA                     | −0.1062550  | <0.01| 0.6416590    | −0.0514570 (.452) |

If age was not significant in a model, the coefficients were recalculated after excluding. Data are coefficient (P value).

| Significance at P < 0.05. Models are adjusted for education and study cohort effects. Including interaction terms between APOE status and age, age, sex, and education one at a time to those regression models showed no significant interaction (P > 0.3). |

**DISCUSSION**

Although the APOE e4 allele is the strongest genetic sporadic AD risk factor accounting for most of AD genetic-related risk and is associated with an earlier clinical onset of dementia and preclinical biomarker changes, we did not find brain volume differences between APOE e4 carriers and noncarriers.

Here we studied the association between the APOE genotype and brain structure in a large cohort of subjects with a wide age range recruited from the general population whose MR imaging scans were obtained by using a standardized sequence in all subjects. We quantified structural brain changes by using 2 approaches: 1) an ROI approach, guided by previous findings; and 2) a pattern-based analysis by using 2 machine-learning-based summary indices. The imaging indices, the SPARE-AD and the SPARE-BA, were developed to quantify AD- and age-related brain changes, respectively. SPARE-AD has been shown to predict early AD-related changes and preclinical dementia.

The mechanisms underlying the white matter microstructural changes are still not well-understood, but it is possible that detection of more subtle associations between APOE and brain structure in preclinical dementia requires microstructural assessment.

Limitations of our study include the use of imputed genotype data from single nucleotide polymorphism (SNP) arrays and not a specific assay for APOE to determine the APOE genotype, the basis of the current AD biomarker model that predicts occurrence of amyloid deposition before brain atrophy, a finding of brain atrophy in the third decade of life would be unlikely.

Previous studies have reported lower hippocampal, orbitofrontal, and entorhinal volumes in subjects with APOE e4 in the early decades of life. The possible reasons for conflicting results could be differences in selection of the sample, the sample size, or processing pipelines of the MR imaging scans. Another potential explanation is that negative results are less likely to be reported than positive ones. Our study included a similar, or even larger, sample size than that in previous studies and applied sensitive methods to detect even subtle MR imaging changes associated with early AD-related changes and aging. However, it is possible that differences in functional changes associated with the APOE genotype at a younger age, as reported previously, precede structural changes and potentially even widespread amyloid deposition, though this hypothesis still requires larger samples to validate initial reports based on small-sized cohorts.

In recent work, AD pathology from preclinical-to-clinical stages was associated with a decrease in the metabolism of the posterior cingulate cortex, even before any sign of AD. The appearance of hypometabolism before clinical change could vary depending on cognitive reserve. The results on cognitive reserve and APOE are controversial in the literature. However, APOE does not seem to modulate the effect of cognitive reserve on cognitive function. Due to the lack of functional imaging measures in our cohort, we could not evaluate the presence of these changes in the framework of SHIP.
CONCLUSIONS
Our study indicates that measurable APOE-related brain atrophy does not occur during early adulthood and midlife and suggests that APOE-related MR imaging atrophy may only be present later in life, more proximal to clinical disease onset.

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