Multimodal characterization of older *APOE2* carriers reveals selective reduction of amyloid load

Michel J. Grothe, PhD
Sylvia Villeneuve, PhD
Martin Dyrba, PhD
David Bartrés-Faz, PhD
Miranka Wirth, PhD
For the Alzheimer's Disease Neuroimaging Initiative

Correspondence to Dr. Grothe: michel.grothe@dzne.de

ABSTRACT

Objective: To comprehensively assess neurobiological effects of the protective *APOE2* allele in the aged brain using a cross-sectional multimodal neuroimaging approach.

Methods: Multimodal neuroimaging data were obtained from a total of 572 older individuals without dementia (cognitively normal and mild cognitive impairment) enrolled in the Alzheimer's Disease Neuroimaging Initiative and included assessments of regional amyloid load with AV45-PET, glucose metabolism with fluorodeoxyglucose-PET, and gray matter volume with structural MRI. Imaging indexes of *APOE2* carriers were contrasted to risk-neutral *APOE3* homozygotes, and analyses were controlled for age, sex, education, and clinical diagnosis. Additional models examined genotype-specific effects of age on the imaging markers.

Results: In region-of-interest–based analyses, *APOE2* carriers had significantly less precuneal amyloid pathology and did not show the typical age-related increase in amyloid load, although the age × genotype interaction was only trend-level significant. In contrast, parietal metabolism and hippocampal volume did not differ between *APOE2* and *APOE3* genotypes, and both groups showed comparable negative effects of age on these markers. The amyloid specificity of *APOE2*-related brain changes was corroborated in 2 complementary analyses: spatially unbiased voxel-wise analyses showing widespread reductions in amyloid deposition but no differences in gray matter volume or metabolism and an analysis of CSF-based biomarkers showing a significant effect on amyloid but not on tau pathology.

Conclusions: Regarding the range of Alzheimer disease biomarkers considered in the present study, the *APOE2* allele appears to have a relatively selective effect on reduced accumulation of amyloid pathology in the aged brain. ***Neurology*® 2017;88:569–576**

GLOSSARY

Aβ = β-amyloid; **AD** = Alzheimer disease; **ADNI** = Alzheimer's Disease Neuroimaging Initiative; **ANCOVA** = analysis of covariance; **CN** = cognitively normal; **FDG** = fluorodeoxyglucose; **GM** = gray matter; **MCI** = mild cognitive impairment; **PiB** = Pittsburgh compound B; **p-tau** = phosphorylated tau; **ROI** = region of interest; **t-tau** = total tau.

The *APOE2* allele is one of the best described gene variants associated with a reduced risk for late-life cognitive decline and Alzheimer disease (AD) dementia.[1–4] Previous research aimed at understanding the neurobiological mechanisms by which the *APOE* gene might modify AD risk has focused mainly on the detrimental effects of the *APOE4* risk allele,[5–8] whereas the putative protective effects of *APOE2* have received far less attention.[9] Principally, the protective effect of *APOE2* could be mediated by a direct interaction with AD pathology such as reduced accumulation of cortical amyloid deposits or neurofibrillary changes[6,7,10–13] but also by more general positive effects on brain structure or function that may increase the resilience of the brain against AD pathology.

Supplemental data at Neurology.org

From the German Center for Neurodegenerative Diseases (M.J.G., M.D.), Rostock, Germany; Douglas Mental Health University Institute (S.V.), Research Centre, Verdun; Department of Psychiatry (S.V.), McGill University, Montreal, Quebec, Canada; Department of Medicine (D.B.-F.), Faculty of Medicine and Health Sciences, University of Barcelona, Spain; and NeuroCure Clinical Research Center (M.W.) and Department of Neurology, Charité–Universitätsmedizin Berlin, Germany.

Data used in preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu/). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in analysis or writing of this report. A complete listing of ADNI investigators can be found in the coinvestigators list at Neurology.org.

Go to Neurology.org for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

To date, very few neuroimaging studies have specifically examined *APOE2* effects on cortical amyloid pathology[12] or brain structure[11,14,15] and function[16] in older persons, and some of these studies yielded contradictory findings. Moreover, each of these studies was limited to the assessment of a single imaging modality; thus, the specificity of the detected *APOE2* effect for the examined aspect of brain integrity remains unknown.

Here, we used a large, multimodal neuroimaging dataset to comprehensively study the potential protective effects of the *APOE2* allele on cortical amyloid deposition (using AV45-PET), brain structure (structural MRI), and metabolic function (fluorodeoxyglucose [FDG]-PET) within the same sample of older individuals without dementia.

METHODS

Participants. All data used in the present study were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI), a multicenter longitudinal study collecting clinical, neuroimaging, and other biological markers of AD progression in cognitively normal (CN) older individuals and patients with mild cognitive impairment (MCI) and early AD dementia (adni-info.org). The present study sample consisted of 572 older individuals without dementia from the ADNI-GO and ADNI-2 cohorts including 176 CN participants and 396 participants with MCI. Detailed diagnostic criteria have been reported previously[17] and are published on the ADNI website (adni.loni.usc.edu/methods/). Both ADNI-specific categories of early MCI and late MCI, which differ only in the applied cutoff for objective memory impairment, were included in the MCI sample. Eligibility criteria for the present study included availability of *APOE* genotyping and availability of AV45-PET, FDG-PET, and high-resolution structural MRI acquisitions from the same study time point.

APOE genotype was determined by genotyping the 2 single nucleotide polymorphisms that define the *APOE* ε2, ε3, and ε4 alleles (rs429358, rs7412) with DNA extracted by Cogenics from a 3-mL aliquot of EDTA blood (adni.loni.usc.edu/data-samples/genetic-data/).

The total sample of older individuals without dementia was stratified according to the following *APOE* genotypes: ε2/ε3 (*APOE2*; n = 50, 8.9%), ε3/ε3 (*APOE3*; n = 282, 50%), and combined ε3/ε4 or ε4/ε4 (*APOE4*, n = 232, 41.1%). The very rare ε2/ε2 genotype was not present in our study sample. To avoid confounding effects of the *APOE4* allele, individuals with an ε2/ε4 genotype (8 MCI, 0 CN) were excluded from analyses. In this study, we focused on differences between *APOE2* and *APOE3* groups, given that *APOE4* effects have been well documented in several previous studies, including 2 recent multimodal imaging studies on overlapping samples from the ADNI cohort.[18,19]

Memory function of the different *APOE* groups was characterized with a neuropsychometric composite score that has been described in detail previously.[20] In addition to the baseline data, 2-year longitudinal follow-up (24.5 ± 2.1 months) of composite memory score was available for 84% of the study sample.

Standard protocol approvals, registrations, and patient consents. Data collection and sharing in ADNI were approved by the Institutional Review Board of each participating institution, and written informed consent was obtained from all participants.

Imaging data. Acquisition and standardized preprocessing steps of the multicentric MRI and PET imaging data in ADNI have been reported previously[17] and are described in detail on the ADNI website (adni.loni.usc.edu/methods/). Briefly, structural MRI data were acquired on 3T scanning platforms using T1-weighted sagittal 3-dimensional magnetization-prepared rapid-acquisition gradient echo sequences. AV45-PET scans were acquired during a 50- to 70-minute interval following a 370-MBq bolus injection of AV45. FDG-PET scans were acquired during a 30- to 60-minute interval following a 185-MBq bolus injection of [^{18}F]-FDG. All ADNI imaging data undergo standardized preprocessing steps aimed at increasing data uniformity across the multicenter scanner platforms.

Imaging data were processed with SPM8 (Wellcome Trust Center for Neuroimaging) and the associated VBM8 toolbox (dbm.neuro.uni-jena.de/vbm/) implemented in MATLAB R2013a (MathWorks, Natick, MA) as described in detail previously.[17] Image processing involved tissue-type segmentation of the structural MRI scans, followed by a high-dimensional registration to an aging/AD-specific reference template[21] and spatial normalization of the gray matter (GM) tissue maps (with modulation of voxel values). AV45- and FDG-PET scans were rigidly coregistered to the corresponding structural MRI scan, corrected for partial volume effects,[22] and spatially normalized with the registration parameters from the corresponding MRI scans.

The distinct imaging signals were sampled from regions of interest (ROIs) that are sensitive for AD-related alterations in the respective imaging modalities (figure 1), i.e., the precuneus for AV45-PET,[23] a composite parietal cortical ROI for FDG-PET,[24] and the hippocampus for GM volume. AV45- and FDG-PET uptake means were converted to standard uptake value ratios by proportional scaling to signal within the whole cerebellum and pons, respectively, and hippocampal GM volumes were scaled by the total intracranial volume. More detailed information on ROI definition is provided in appendix e-1 at Neurology.org.

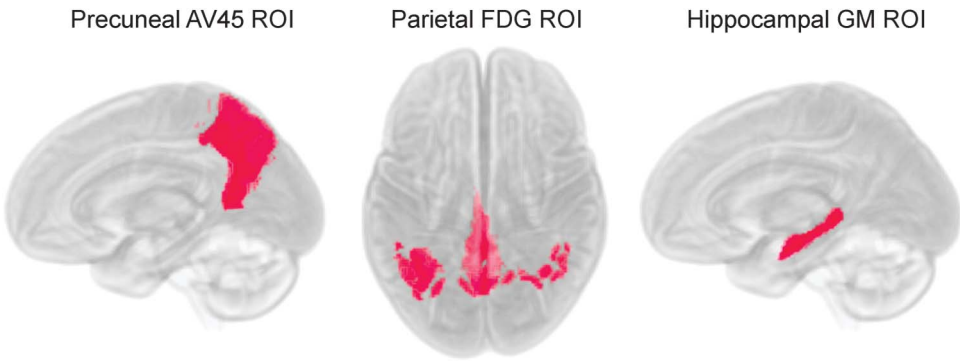
Statistical analysis. Demographic and baseline clinical characteristics were compared between genotypic groups by use of 2-sample *t* tests for parametric variables and the Fisher exact test for binary variables. Statistical significance of differences in imaging markers and 2-year change in memory function between the *APOE2* and *APOE3* groups were assessed with analysis of covariance (ANCOVA) models controlled for age, sex, education, and clinical diagnosis.

Effects of age on each imaging marker were assessed separately for each genotypic group with multiple linear regression controlled for sex, education, and clinical diagnosis. Additional models included a genotype × age interaction term to assess the statistical significance of differences in regression slopes between genotypic groups. Complementary analyses using dichotomous amyloid status instead of continuous standard uptake value ratio as the outcome variable are reported in appendix e-2. Analyses were carried out with the software package IBM SPSS Statistics version 21 (IBM, Armonk, NY).

Complementary analyses. In 2 sets of secondary analyses, we aimed to corroborate our primary ROI-based findings of significant main effects of *APOE2* genotype.

First, differences between *APOE2* and *APOE3* groups were assessed with voxel-wise tests that are independent of the a priori selection of modality-specific ROIs. Voxel-wise analyses used analog ANCOVA models controlled for age, sex, education, and clinical diagnosis. Preprocessed imaging data were smoothed

Figure 1 Illustration of the modality-specific ROIs



Anatomical locations of the modality-specific regions of interest (ROIs) are depicted in representative views of the study template. More detailed information on ROI definition is provided in appendix e-1. FDG = fluorodeoxyglucose; GM = gray matter.

with a gaussian smoothing kernel of 8 mm, and analyses were restricted to a GM mask of the reference template. AV45- and FDG-PET maps were proportionately scaled to whole cerebellum and pons uptake values, respectively, and analyses of GM maps included total intracranial volume as an additional nuisance regressor. Results were assessed at a voxel-wise statistical threshold of $p < 0.05$, corrected for multiple comparisons using the false discovery rate.

Second, genotypic group differences were also assessed with CSF biomarkers. Complete CSF measures of β-amyloid $(A\beta)_{42}$, phosphorylated (p-tau), and total tau (t-tau) from the same study time point were available for ≈85% of the included study sample. Methods for CSF biomarker quantification in the ADNI cohort are based on the xMAP Luminex platform and Innogenetics/Fujirebio AlzBio3 immunoassay kits and are described in detail elsewhere[25] (adni.loni.usc.edu/methods/). Genotypic group differences in CSF $A\beta_{42}$, p-tau, and t-tau were assessed with ANCOVA models analogous to those for the imaging markers.

Table 1 Sample characteristics

	APOE2	*APOE3*
No.	50	282
Age, y	73.0 ± 6.9	73.3 ± 7.3
Sex, M/F	28/22	147/135
Education, y	16.4 ± 2.7	16.4 ± 2.6
Race, AN/A/B/W/M	0/1/3/46/0	2/6/12/258/4
Diagnosis, CN/MCI	23/27	103/179
MMSE	28.5 ± 1.6	28.7 ± 1.4
Memory composite	0.77 ± 0.75	0.74 ± 0.69
Change in memory composite[a]	0.10 ± 0.32	0.06 ± 0.45

Abbreviations: A = Asian; AN = American Indian or Alaskan Native; B = black or African American; CN = cognitively normal; M = more than one race; MCI = mild cognitive impairment; MMSE = Mini-Mental State Examination; W = white.
Table shows sample size (n), demographics, proportion of individuals with a clinical diagnosis of CN or MCI, and global (MMSE) and memory-specific (memory composite score[20]) neuropsychological test performance for the *APOE2* (ε2/ε3) and *APOE3* (ε3/ε3) genotype groups. Numbers indicate group mean ± SD or number of individuals in each category for bivariate variables.
[a] Two-year longitudinal follow-up information was available for only a subset of participants ($n_{APOE2} = 47$; $n_{APOE3} = 233$; average follow-up: 24.5 ± 2.1 months).

RESULTS Demographic and clinical characteristics of the study sample are summarized in table 1. *APOE2* carriers did not differ significantly from the *APOE3* genotype in any of the assessed demographic or baseline clinical variables. Both groups showed stable memory performance over the 2-year follow-up period, and changes in memory score did not differ between the 2 groups ($p = 0.68$).

***APOE2* effects on multimodal imaging markers.** Mean values of precuneal amyloid load, parietal glucose metabolism, and hippocampal volume for each of the genotypic groups are summarized in table 2. Precuneal amyloid load was significantly lower in *APOE2* carriers compared to the *APOE3* group ($p = 0.009$). In contrast, parietal metabolism ($p = 0.41$) and hippocampal volume ($p = 0.92$) did not differ significantly between the 2 groups.

Figure 2 shows the different imaging markers plotted against age with fitted linear regression lines for each genotypic group. Precuneal amyloid load was independently associated with age in the *APOE3* ($\beta = 0.35$, $p < 0.001$) but not in the *APOE2* ($\beta = 0.10$, $p = 0.49$) group, although the difference in slope estimates was only trend-level significant ($p = 0.06$). In contrast, parietal hypometabolism and hippocampal volume showed similar negative associations with age in both genotypic groups, and differences in regression slopes were not significant ($p > 0.45$).

All of these findings remained unchanged when the study sample was limited to white individuals.

Voxel-wise findings. Voxel-wise analyses across the whole brain confirmed a reduced amyloid load in *APOE2* carriers compared to the *APOE3* group that mapped to large parts of the posterior parietal, temporal, and frontal neocortex (figure 3). In contrast, no evidence of higher metabolism or GM volume in *APOE2* carriers compared to the *APOE3* group was found throughout the brain.

Table 2 Genotypic group means of multimodal imaging and CSF biomarkers

	APOE2	APOE3	d
Imaging markers			
No.	50	282	
Precuneal AV45 SUVR	0.80 ± 0.26[a]	0.96 ± 0.40	−0.42
Parietal FDG SUVR	2.05 ± 0.23	2.08 ± 0.25	−0.10
Hippocampal volume	3.60 ± 0.42	3.58 ± 0.34	0.06
CSF markers[b]			
No.	42	246	
$A\beta_{42}$	216 ± 47[a]	199 ± 48	0.36
p-tau	30 ± 16	34 ± 18	−0.25
t-tau	61 ± 32	69 ± 39	−0.21

Abbreviations: Aβ = β-amyloid; *d* = Cohen *d* effect size; FDG = fluorodeoxyglucose; p-tau = phosphorylated tau; SUVR = standard uptake value ratios; t-tau = total tau.
[a] Significantly different from *APOE3* ($p < 0.05$) in an analysis of covariance model controlled for age, sex, education, and clinical diagnosis.
[b] CSF biomarkers were available for only a subset of participants.

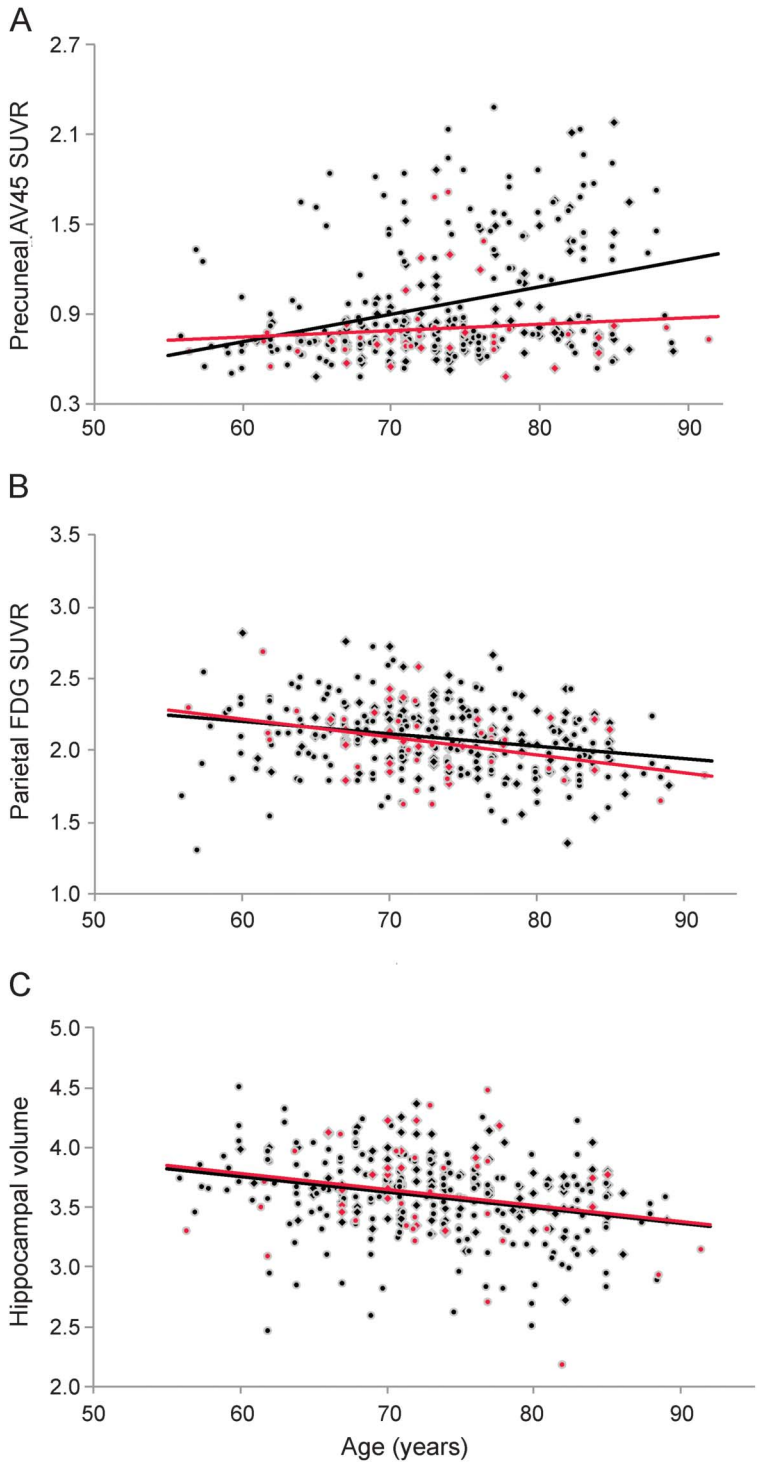
***APOE2* effects on CSF markers.** In analogy to the amyloid specificity of the imaging marker findings, *APOE2* carriers had significantly higher CSF $A\beta_{42}$ levels compared to the *APOE3* group ($p = 0.02$), whereas levels of p-tau ($p = 0.15$) and t-tau ($p = 0.23$) were not significantly different (table 2).

DISCUSSION We used multimodal imaging data from a large cohort of older individuals without dementia to investigate differences in neuroimaging markers of molecular (amyloid), structural (GM volume), and functional (glucose metabolism) brain health between *APOE2* carriers and those homozygous for the *APOE3* allele. We found that older individuals without dementia who carry an *APOE2* allele had less precuneal amyloid pathology and did not show the typical age-related increase in amyloid load (although the age × genotype interaction was only trend-level significant). On the other hand, imaging markers of brain structure and function in AD-susceptible regions, including hippocampus volume and parietal metabolism, did not differ significantly between the *APOE2* and *APOE3* genotypes, and both groups showed comparable negative effects of age on these markers. The specificity of *APOE2*-related brain changes for amyloid pathology was reinforced by complementary voxel-wise analyses that are independent of the a priori selection of AD-typical ROIs, as well as by an analysis of CSF biomarkers that showed a significant *APOE2* effect on reduced amyloid pathology but not on markers of tau pathology.

Our study demonstrated a protective role of the *APOE2* allele on cortical amyloid deposits in older individuals without dementia. In contrast to the *APOE4* AD risk allele, neuroimaging studies assessing brain changes associated with the protective *APOE2* allele are still rare. Only one previous study used amyloid PET imaging (Pittsburgh compound B [PiB]-PET) to investigate *APOE2* effects on quantitative indexes of cerebral amyloid load in 241 CN older persons, including 29 *APOE2* carriers.[12] However, when controlling for the effect of *APOE4*, i.e., specifically assessing differences between *APOE2* carriers and *APOE3* homozygotes, the effect of *APOE2* carrier status on global cortical PiB-PET uptake values or their relation with age was not statistically significant. More robust in vivo evidence for an amyloid-protective effect of the *APOE2* allele comes from a recent meta-analytic study of dichotomous amyloid status derived from pooled amyloid-PET or CSF $A\beta_{42}$ data across several cohorts totaling 2,130 genotyped older persons with normal cognition and 2,832 with MCI.[8] In both diagnostic groups, differential age-related increases in the prevalence of amyloid positivity were found between all *APOE* genotypes, being lowest in *APOE2* carriers, intermediate in *APOE3* homozygotes, and highest in *APOE4* carriers. This also translated into significant group differences in the prevalence of amyloid positivity between *APOE2* carriers and *APOE3* homozygotes at the median age of 70 years. This study also indicated that increases in amyloid pathology associated with the *APOE4* allele were much more pronounced than decreases in amyloid pathology associated with the *APOE2* allele, possibly explaining the unexpected negative findings in the earlier PiB-PET study.[12] Interestingly, this differential effect on amyloid load also parallels differences in effect size for the allele-dependent risk of cognitive decline[3,4] and AD dementia[2] and could be related to differences in the regulation of amyloid clearance between the respective APOE isoforms.[26]

The examination of amyloid-PET data alone cannot answer the question of whether neurobiological effects of the protective *APOE2* allele are specific for reduced amyloid pathology or similarly extend to positive effects on brain structure or function that may increase the resilience of the brain against AD pathology. Our findings demonstrate a relatively specific effect of *APOE2* on cortical amyloid deposition in the absence of any notable effect on glucose metabolism or GM volume. To the best of our knowledge, *APOE2* effects on neuronal metabolism as measured by FDG-PET have not been studied before, and only a small number of MRI studies have specifically examined *APOE2* effects on brain structure or function in older age. However, the findings from these studies are inconclusive, with some studies showing (marginally significant) larger volumes of the hippocampus[15] or other temporal lobe structures[27] in *APOE2* carriers and others finding no volume differences[14] or finding only differences in longitudinal

Figure 2 Effects of age and *APOE* genotype on multimodal imaging markers



Precuneal AV45 standard uptake value ratios (SUVRs) (A), parietal fluorodeoxyglucose (FDG) SUVR (B), and hippocampal volumes (C) are plotted against age for *APOE3* (black) and *APOE2* (red) genotypic groups. Separate linear regression lines are fitted for each group. Cognitively normal individuals are represented by diamonds; those with mild cognitive impairment, by circles.

atrophy rates, not in baseline volumes.[11] A recent functional MRI study indicated a protective effect of the *APOE2* allele on age-related decreases in brain function,[16] but other studies in younger populations found *APOE2*-related activity changes in functional MRI data that were comparable to those of the *APOE4* allele and thus not compatible with a protective effect.[9,28]

Several unimodal imaging studies reported detrimental effects of the *APOE4* allele on cortical glucose metabolism and hippocampal volume,[5] which has been interpreted in light of evidence for amyloid-independent mechanisms of *APOE*-mediated dementia risk.[29,30] However, more recent multimodal imaging studies could demonstrate that the predominant effect of *APOE4* genotype relates to increased cortical amyloid load,[18,31] which possibly mediates downstream effects on neurodegeneration and dysfunction.[32] Here, we demonstrate a similar specificity, in the opposite direction, for brain changes associated with the *APOE2* allele. Our findings do not exclude the possibility of amyloid-independent *APOE2* effects on brain structure and function in younger age or subtle effects on brain characteristics that may not be captured by the imaging markers used in our study.[16,28,29,33,34] However, within the context of most commonly used biomarkers for characterizing different categories of AD-relevant changes in the aging brain,[35] the predominant pathway of *APOE2*-mediated effects appears to relate to cortical amyloid processing.

Supporting evidence for an amyloid-specific effect of *APOE2* comes from a recent multicohort study of CSF biomarkers.[7] Thus, across a large sample of 1,233 individuals, *APOE2* carrier status was significantly associated with higher CSF $A\beta_{42}$ levels, but not t-tau or p-tau levels, after controlling for age, sex, and *APOE4*. Together with the significantly decreased risk of cognitive decline and AD dementia in older persons with low levels of cerebral amyloid load,[36] our data suggest that reduced amyloid pathology may be one of the main neurobiological correlates underlying the clinically protective effect of the *APOE2* allele. The decreased risk for cognitive decline in low-amyloid individuals could also be replicated in our study cohort (appendix e-3). However, the full mediation model could not be explicitly tested in our study, given that the clinically protective effect of the *APOE2* allele could not be established within the 2-year neuropsychological follow-up available for our study cohort. Previous demonstrations of a clinically protective effect of the *APOE2* allele in individuals without dementia included both larger sample sizes and considerably longer follow-up periods.[3,4]

Although CSF tau biomarkers are often used interchangeably with imaging markers of parietal hypometabolism or hippocampal atrophy in the context of neuronal injury/neurodegeneration markers of AD,[35] recent comparisons demonstrate relatively poor agreement between the different types of biomarkers,[37] indicating that they track at least partially

Figure 3 Voxel-wise analysis of reduced amyloid load in older *APOE2* carriers without dementia

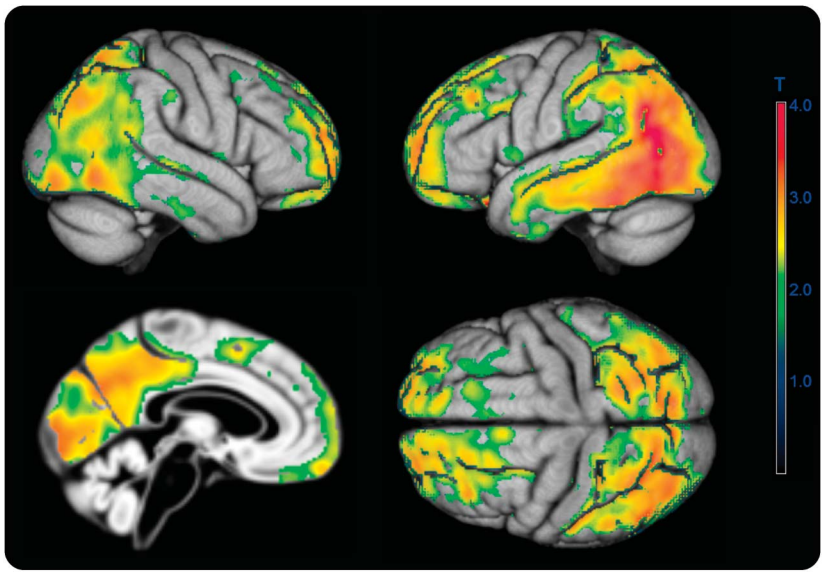


Figure shows results of a voxel-wise 2-sample *t* test assessing reduced AV45 standard uptake value ratios (SUVRs) in *APOE2* carriers compared to the *APOE3* control group across the entire brain while controlling for age, sex, education, and clinical diagnosis (cognitively normal or mild cognitive impairment). Statistical map was thresholded at $p < 0.05$, corrected for multiple voxel-wise comparisons with the false discovery rate. Analogous analyses for fluorodeoxyglucose SUVR or gray matter volume did not reveal any significant effects.

independent pathophysiological processes in the aging brain. However, according to our findings, none of these appear to be significantly altered by the presence of an *APOE2* allele.

Our study has some limitations. Although the analyzed cohort was exceptionally large for a multimodal imaging study involving multitracer PET and MRI data, the sample size for the *APOE2* group was limited by the relative rarity of the *APOE2* allele.[2,9] Thus, statistical power may have been too low to reveal a significant age × genotype interaction effect on amyloid load, although differences in slope estimates were quite pronounced between genotypic groups. In contrast, effect sizes for *APOE2* effects on MRI- and FDG-PET–derived imaging markers indicated negligible effects on these modalities, which were at least 4 times weaker than the effect on amyloid, suggesting that low statistical power is not a likely explanation for these negative findings. Because of the limited number of *APOE2* carriers within the whole sample, effects on the different imaging variables were assessed across pooled diagnostic categories (CN and MCI). This approach is commonly used in settings in which sample size is critical such as in most genome-wide association studies[38] and has also been used in several previous candidate gene studies.[39,40] Controlling the analyses for clinical diagnosis as a confound ensures that the detected genetic effects are not attributable to diagnostic group differences.[38,40] However, we did not assess additional genotype × diagnosis interaction effects in this study. Finally, the cross-sectional nature of our data does not allow estimation of individual brain changes with age, which may be a more sensitive approach for detecting differing brain trajectories in aging *APOE2* carriers.[11] Our analysis of genotype-specific age effects on neuroimaging markers should be followed up with longitudinal imaging data.

Using a multimodal imaging approach to comprehensively study *APOE2* effects in a large sample of older individuals without dementia, our study expands on previous unimodal imaging studies and provides evidence that the *APOE2* allele has a relatively selective effect on reduced accumulation of amyloid pathology compared to conventional imaging markers of AD-relevant changes in brain structure and function. These findings add important information to our understanding of the neurobiological mechanisms that may underlie the well-established protective effect of this allele against age-related cognitive decline and AD dementia.

AUTHOR CONTRIBUTIONS

Michel J. Grothe: study concept, analysis and interpretation of data, drafting/revising the manuscript for content. Sylvia Villeneuve: study concept, interpretation of data, drafting/revising the manuscript for content. Martin Dyrba: analysis of data, contribution of analytic tools. David Bartrés-Faz and Miranka Wirth: study concept, interpretation of data, drafting/revising the manuscript for content.

STUDY FUNDING

Data collection and sharing for this project were funded by the ADNI (NIH grant U01 AG024904) and Department of Defense ADNI (award no. W81XWH-12-2-0012). The ADNI was launched in 2003 by the

National Institute on Aging, the National Institute of Biomedical Imaging and Bioengineering, the Food and Drug Administration, private pharmaceutical companies, and nonprofit organizations as a $60 million, 5-year public-private partnership. ADNI is funded by the National Institute on Aging, the National Institute of Biomedical Imaging and Bioengineering, and through generous contributions from the following: Alzheimer's Association; Alzheimer's Drug Discovery Foundation; Araclon Biotech; BioClinica, Inc; Biogen Idec Inc; Bristol-Myers Squibb Co; CereSpir, Inc; Eisai Inc; Elan Pharmaceuticals, Inc; Eli Lilly and Co; EuroImmun; F. Hoffmann-La Roche Ltd and its affiliated company Genentech, Inc; Fujirebio; GE Healthcare; IXICO Ltd; Janssen Alzheimer Immunotherapy Research & Development, LLC; Johnson & Johnson Pharmaceutical Research & Development LLC; Lumosity; Lundbeck; Merck & Co, Inc; Meso Scale Diagnostics, LLC; NeuroRx Research; Neurotrack Technologies; Novartis Pharmaceuticals Corp; Pfizer Inc; Piramal Imaging; Servier; Takeda Pharmaceutical Co; and Transition Therapeutics. The Canadian Institutes of Health Research is providing funds to support ADNI clinical sites in Canada. Private sector contributions are facilitated by the Foundation for the National Institutes of Health (fnih.org). The grantee organization is the Northern California Institute for Research and Education, and the study is coordinated by the Alzheimer's Disease Cooperative Study at the University of California, San Diego. ADNI data are disseminated by the Laboratory for Neuroimaging at the University of Southern California.

DISCLOSURE

The authors report no disclosures relevant to the manuscript. Go to Neurology.org for full disclosures.

Received April 30, 2016. Accepted in final form November 16, 2016.

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