Interaction between years of education and *APOE* ε4 status on frontal and temporal metabolism

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ABSTRACT

Objective: To examine interactions between years of education and *APOE* ε4 status on gray matter volume and metabolism in cognitively healthy participants.

Methods: Seventy-two healthy participants (28 *APOE* ε4 carriers and 44 noncarriers; from 23 to 84 years of age) with FDG-PET and structural MRI were included. A subgroup also underwent florbetapir-PET. We tested the interaction effect between years of education and *APOE* ε4 status (carrier vs noncarrier) on FDG-PET and structural MRI within the whole brain (voxel-wise) adjusting for age and sex. Computed florbetapir standardized uptake value ratios were used for complementary analyses.

Results: We found an interaction between years of education and *APOE* ε4 status on frontotemporal FDG-PET metabolism, such that higher education was positively related to frontotemporal metabolism only in *APOE* ε4 carriers. Complementary analyses revealed that (1) this interaction was independent from amyloid load; (2) increased metabolism in *APOE* ε4 carriers in this region correlated with episodic memory performances; (3) lower educated *APOE* ε4 carriers showed decreased metabolism relative to noncarriers in medial temporal and prefrontal areas, while higher educated carriers were comparable to noncarriers in these areas and showed increased metabolism in the middle temporal lobe.

Conclusions: Our results showed that education may counteract the effects of *APOE* ε4 on metabolism independently of amyloid deposition. Higher metabolism in higher (compared to lower) educated *APOE* ε4 carriers was found in regions that sustain episodic memory. Overall, our results point to education as a protective factor that may help to postpone cognitive changes in *APOE* ε4 carriers. *Neurology*® 2015;85:1392–1399

GLOSSARY

AD = Alzheimer disease; **IMAP** = Imagerie Multimodale de la maladie d'Alzheimer à un stade Précoce; **MCI** = mild cognitive impairment; **PVE** = partial volume effects; **SPM** = statistical parametric mapping; **SUVR** = standardized uptake value ratio.

The allelic variation ε4 of *APOE* is the most influential genetic risk factor for sporadic Alzheimer disease (AD).[1–3] *APOE* ε4 effect on cognitive impairment or dementia risk appears to be diminished by exposure to enriched environments such as that provided by education.[4–6] In line with this, recent neuroimaging investigations provided promising evidence that, in older adults with normal cognition, *APOE* ε4 effects on Aβ deposition can be mitigated by cognitive activities.[7] While both *APOE* ε4[8] and education[9,10] have been shown to impact brain structure (gray matter volume) and function (FDG-PET) in cognitively normal participants, it is unknown whether *APOE* ε4 effects on brain structure and function could be mitigated by education as reported for Aβ deposition. Our main goal in the present study was therefore to assess the interaction effect

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between *APOE* ε4 status (carrier vs noncarrier) and years of education on brain gray matter volume and FDG-PET metabolism in cognitively normal individuals.

METHODS Participants. A total of 72 participants, 28 *APOE* ε4 carriers and 44 noncarriers aged 23–84 years, were recruited from the Imagerie Multimodale de la maladie d'Alzheimer à un stade Précoce (IMAP) Study (Caen, France) (table 1 shows demographic data). All participants underwent clinical and neuropsychological examinations. Because of the multimodal approach of the present study, we selected participants who had both structural MRI and FDG-PET sessions. All participants were screened for lack of abnormalities, as previously described.[9] They had no history or clinical evidence of major neurologic or psychiatric disorder. All participants performed in the normal range in all neuropsychological tests (including tests of episodic memory, working memory, language skills, executive functions, and visuospatial abilities).

Years of education were assessed as years attending school (table 1). *APOE* genotype was identified by restriction isotyping from genomic DNA extracted from frozen leukocytes, amplified by PCR and restricted with *Hha*I.[11]

Standard protocol approvals, registrations, and patient consents. The IMAP study was approved by regional ethics committee (Comité de Protection des Personnes Nord-Ouest III) and is registered with ClinicalTrials.gov (number NCT01638949). All participants gave written consent for participation before the scans.

Imaging protocol. The study participants were examined on the same MRI and PET scans at the Cyceron center (Caen, France). A subsample of 54 individuals (out of the 72 participants included in the present study), including 19 *APOE* ε4 carriers and 35 noncarriers, also had a florbetapir-PET scan (age range 28–84 years, mean age [SD] = 54.6 [14.5] years, 5 Aβ positive [9.4%]). All assessments were obtained within 2 months from neuropsychological evaluation.

Image acquisition and processing. High-resolution TI-weighted anatomical images were acquired on a Philips (Eindhoven, the Netherlands) Achieva 3T scanner (appendix e-1 on the *Neurology*® Web site at Neurology.org). FDG and florbetapir scans were acquired on a Discovery RX VCT 64 PET-CT.

FDG-PET acquisition participants fasted for at least 6 hours before the scanning began. After a 30-minute resting period in a silent environment, ~200 Mbq of FDG were intravenously injected as a bolus. Fifty minutes after injection, a 10-minute PET acquisition scan began. Florbetapir-PET scan lasted 20 minutes, and started 50 minutes after the IV injection of ~4 MBq/Kg of florbetapir (see appendix e-1 for details).

Image preprocessing. Statistical parametric mapping (SPM) 5 software (Wellcome Department of Imaging Neuroscience, Institute of Neurology, London, UK) on MATLAB 7.1 was used for image preprocessing. We followed the methodology described in previous studies of our laboratory.[12] Thus, PET data were corrected for partial volume effects (PVE), the same spatial normalization parameter for MRI and PET dataset was used, and a differential smoothing for each modality was selected in order to equalize the smoothness and obtain equivalent resolution for the 3 imaging modalities.

Structural MRI data. In order to preprocess T1-weighted images we used voxel-based morphometry (VBM5), toolbox (Structural Brain Mapping Group, Christian Gaser, Department of Psychiatry, University of Jean, Germany). MRI data were iteratively segmented. The spatially normalized gray matter segments were modulated correcting for the effects of nonlinear warping (but not affine transformation) so that brain size variation was taken into account. These images were finally smoothed at 10 mm full width at half maximum.

PET data. Florbetapir-PET and FDG-PET data were corrected for PVE using the voxel-by-voxel method in PMOD software. These images were then coregistered onto corresponding MRI and normalized using the normalization parameters from the MRI scan. Finally, they were scaled using the mean PET value of the cerebellar gray matter. Then, resultant maps were smoothed at $9.3 \times 9.3 \times 8.8$ mm.

Standardized uptake value ratios. To obtain quantitative values of florbetapir neocortical retention, standardized uptake value ratios (SUVR) were extracted before the smoothing step in 11 specific brain areas following the methodology described elsewhere.[12]

Statistical analysis. A voxel-wise full factorial design in SPM was carried out in order to test the interaction effect between years of education and *APOE* ε4 status. The influence of age and sex was regressed out in all statistical models. Results were considered significant when $p < 0.005$ (uncorrected) and $K > 1,000$ mm³. In areas where there was a statistically significant years of education × *APOE* ε4 status interaction, values were extracted for complementary analyses in SPSS (Chicago, IL) (see below).

Table 1	Descriptive statistics of the 2 groups involved in the study		
	APOE ε4 carriers	*APOE* ε4 noncarriers	t/χ² (*p* Value)
Mean (SD) age, y	52.68 (17.08)	53.82 (15.80)	0.08 (0.77)
M/F	14/14	29/15	1.8 (0.22)
Mean (SD) education, y	13.71 (3.62)	12.57 (3.54)	1.7 (0.19)
Mean (SD) MMSE	29.28 (0.84)	29.3 (0.78)	0.02 (0.88)
Aβ positive (%)	5 (26)	1 (2)	6.42 (0.02)[a]
Genotype, n (%)	2/4: 2 (7), 3/4: 23 (82), 4/4: 3 (11)	2/3: 8 (18), 3/3: 36 (82)	—

Abbreviation: MMSE = Mini-Mental State Examination.
Percentage of amyloid-positive participants has been calculated over the total number of participants with available florbetapir-PET.
[a] *p* < 0.05.

RESULTS **Years of education × *APOE* ε4 status interaction on MRI and FDG-PET.** No significant interaction was found between years of education and *APOE* status on gray matter volume. As for FDG-PET, a years of education × *APOE* ε4 status interaction was found on bilateral parahippocampal/hippocampal, left middle temporal, and right prefrontal metabolism (figure 1). The interaction effect was such that higher education was related to higher metabolism only in *APOE* ε4 carriers ($r = 0.59$, $p = 0.001$; $r = 0.45$, $p = 0.02$; $r = 0.46$, $p < 0.01$ in the left and right hippocampus and right prefrontal cortex, respectively) but not in the noncarriers (all $p > 0.1$), except for the left hippocampus, where a negative correlation was found in the noncarriers ($r = -0.38$, $p = 0.01$).

Complementary analyses. We conducted 2 sets of complementary statistical analyses. For the first set of analyses, we used the extracted FDG-PET values from the 4 areas showing a significant *APOE* ε4 × years of education interaction so as to (1) assess the reproducibility of our results within different age groups; (2) clarify the role of Aβ deposition in this interaction; and (3) further understand the increased metabolism in frontal and temporal areas as a function of years of education in *APOE* ε4 carriers.

For the second set of analyses, we repeated our voxel-wise analyses using an alternative proxy (i.e., a vocabulary test) as well as using a factor score between the vocabulary test score and years of education with the aim of evaluating the reproducibility of our results.

***APOE* ε4 by years of education interaction within younger and older groups.** Although we considered age as a covariate in our main analyses, we wanted to further confirm that our results were independent of age (i.e., that years of education were associated with increased frontotemporal metabolism at any age). We thus assessed the interaction effect within 2 age groups (age < 55 years and age ≥ 55 years) in SPSS. The interaction was significant within both groups (age < 55 years [n = 35]: $F = 8.11$, $p < 0.008$; age ≥ 55 years [n = 37]: $F = 21.90$, $p < 0.001$).

Amyloid deposition. To test whether the interaction effect of years of education and *APOE* ε4 on gray matter metabolism was related to Aβ deposition, the interaction was assessed introducing neocortical SUVR as a covariate in the model. The interaction effect remained significant ($F = 22.04$, $p = 0.001$), suggesting that it is independent from Aβ deposition. We also recomputed the analysis without the Aβ-positive individuals (identified as described in a previous study),[9] and the interaction remained significant in the subgroup of Aβ-negative individuals ($F = 25.24$; $p = 0.001$).

Potential mechanisms underlying increased frontal and temporal metabolism in higher educated *APOE* ε4 carriers. We aimed to understand increased frontal

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Figure 1   Voxel-wise results and scatterplots of the interaction effect between *APOE* ε4 status and education

— *APOE* ε4 carriers
— Noncarriers
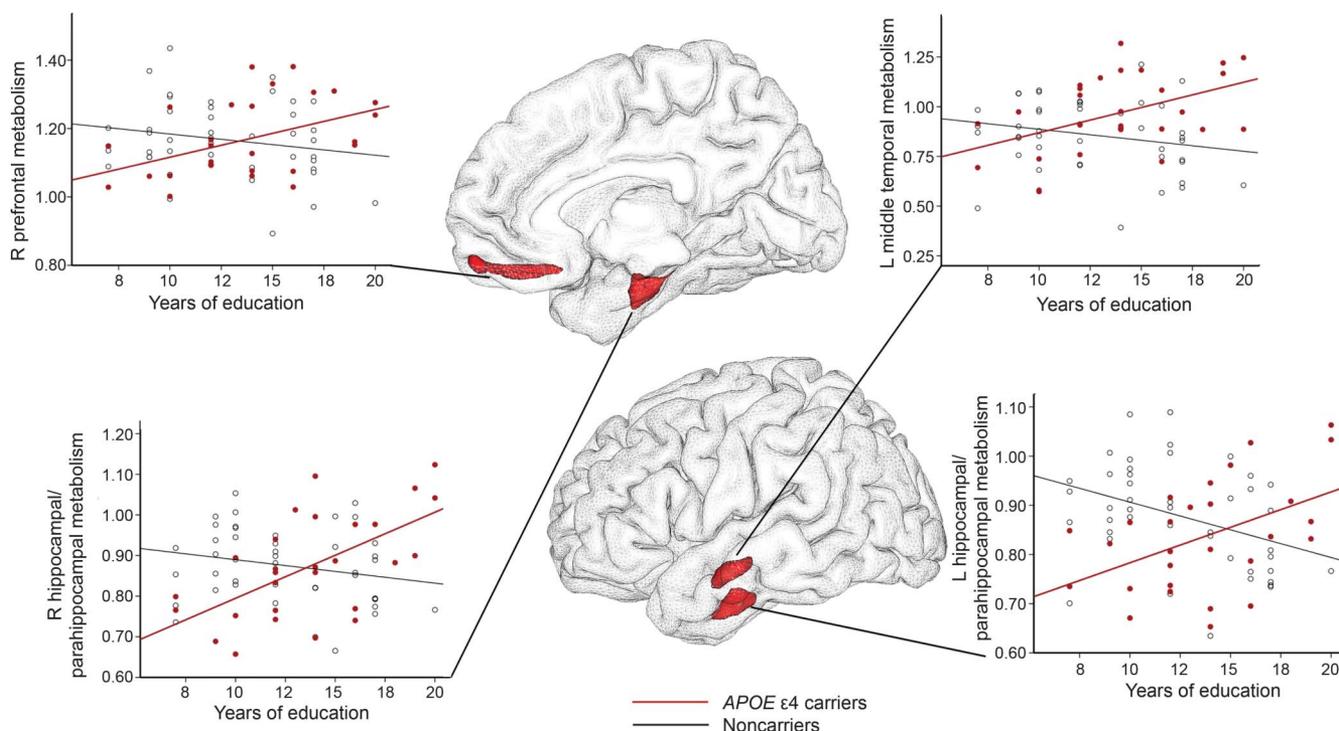
The number of years of education is plotted against the FDG-PET metabolism of each significant cluster.

and temporal metabolism as a function of years of education in *APOE* ε4 carriers. More specifically, we aimed at assessing whether higher educated *APOE* ε4 carriers showed (1) equivalent/preserved frontal and temporal metabolism as compared to noncarriers, which could reflect metabolism maintenance, as predicted by the brain maintenance theory; or (2) increased frontal and temporal metabolism as compared to noncarriers, which may reflect compensatory mechanisms, in line with brain and cognitive reserve theories. Thus, we first compared the extracted FDG-PET values from the areas showing a significant *APOE* ε4 × years of education interaction between noncarriers (the reference group) and the *APOE* ε4 carriers divided into 2 groups of higher (n = 12) and lower (n = 16) educated participants, based on the 50th percentile (years of education >12 or ≤12). The 2 groups did not differ in age ($p = 0.22$) or sex ($p = 0.07$). Then, the same analyses were carried out within each significant cluster (i.e., bilateral hippocampus/parahippocampus, left middle temporal, and right prefrontal) because different education-related effects and mechanisms (e.g., preservation or compensation) may have distinct topographic expression.[13] We used the Dunnett procedure, which allows testing a specific set of pairwise comparisons of interest, being thus less conservative than other multiple comparison tests (i.e., we do not correct for the comparisons that we are not interested in) but still more conservative than pairwise *t* test. When all the areas were considered together, higher educated *APOE* ε4 carriers showed increased metabolism as compared to noncarriers ($t = 0.06$; $p = 0.03$), while no difference was found between lower educated *APOE* ε4 carriers and noncarriers. However, when the analyses were performed within each significant cluster, lower educated *APOE* ε4 carriers showed decreased metabolism as compared to the noncarriers in the right and left parahippocampus/hippocampus areas, and a trend was found in the same direction for the right prefrontal lobe (table 2). In contrast, higher educated *APOE* ε4 carriers showed comparable metabolism to noncarriers in the parahippocampus/hippocampus and right

prefrontal lobe and increased metabolism in the left middle temporal lobe (figure 2).

Finally, we aimed to assess whether the education-related increased metabolism in *APOE* ε4 carriers was related to increased cognitive performance. To assess this question, an episodic memory composite score (*z* score) between verbal (Encodage, Stockage, Récupération)[14] and visual (BEM 144, adapted)[15] memory tests was computed (*APOE* ε4 carriers, mean [SD] = −0.15 [1.14], noncarriers = 0.08 [0.91]). Then, the relationship between this composite score (as the dependent variable) and the metabolism of the areas where there was an *APOE* ε4 by years of education interaction (as the independent variable) was assessed within the *APOE* ε4 carriers in a model including age, sex, and SUVR as covariates. There was a moderate correlation between episodic memory and education-related metabolism in frontal and temporal areas in *APOE* ε4 carriers ($r = 0.55$, $p < 0.03$).

Years of education and vocabulary. To assess the reproducibility of our findings, we recomputed our voxel-wise analyses using, instead of education, vocabulary test performances or a factor score between years of education and a vocabulary test as independent variables, as commonly used in the literature.[16] For the factor score, we computed a factorial analysis in SPSS which allowed us to obtain a factor that reflected the shared variance between years of education and Mill Hill vocabulary test. The analyses with the vocabulary or the factor score yielded the same results as with years of education with the same regions showing a significant interaction at $p < 0.005$.

DISCUSSION Our findings suggest that education might reduce the effects of *APOE* ε4 on metabolism independently of Aβ deposition in cognitively normal adults. Moreover, the education-related increased metabolism in *APOE* ε4 carriers was positively associated with episodic memory performance. Our results thus point to education as a protective factor that may help to postpone cognitive changes in higher educated *APOE* ε4 carriers. More specifically, we found an interaction between *APOE* ε4 status and years of education in frontal and temporal regions such that a positive correlation with years of

Table 2	Dunnett procedure comparing FDG-PET metabolism values between lower and higher educated *APOE* ε4 carriers with noncarriers as the reference group			
Noncarriers group (all)	**R parahippocampus/hippocampus**	**R prefrontal**	**L parahippocampus/hippocampus**	**L middle temporal**
Lower educated *APOE* ε4 carriers	0.06[a]	0.06	0.08[a]	0.01
Higher educated *APOE* ε4 carriers	−0.05	−0.04	0.03	−0.17[a]

The *p* values are SPSS-adjusted.
[a] $p < 0.05$.
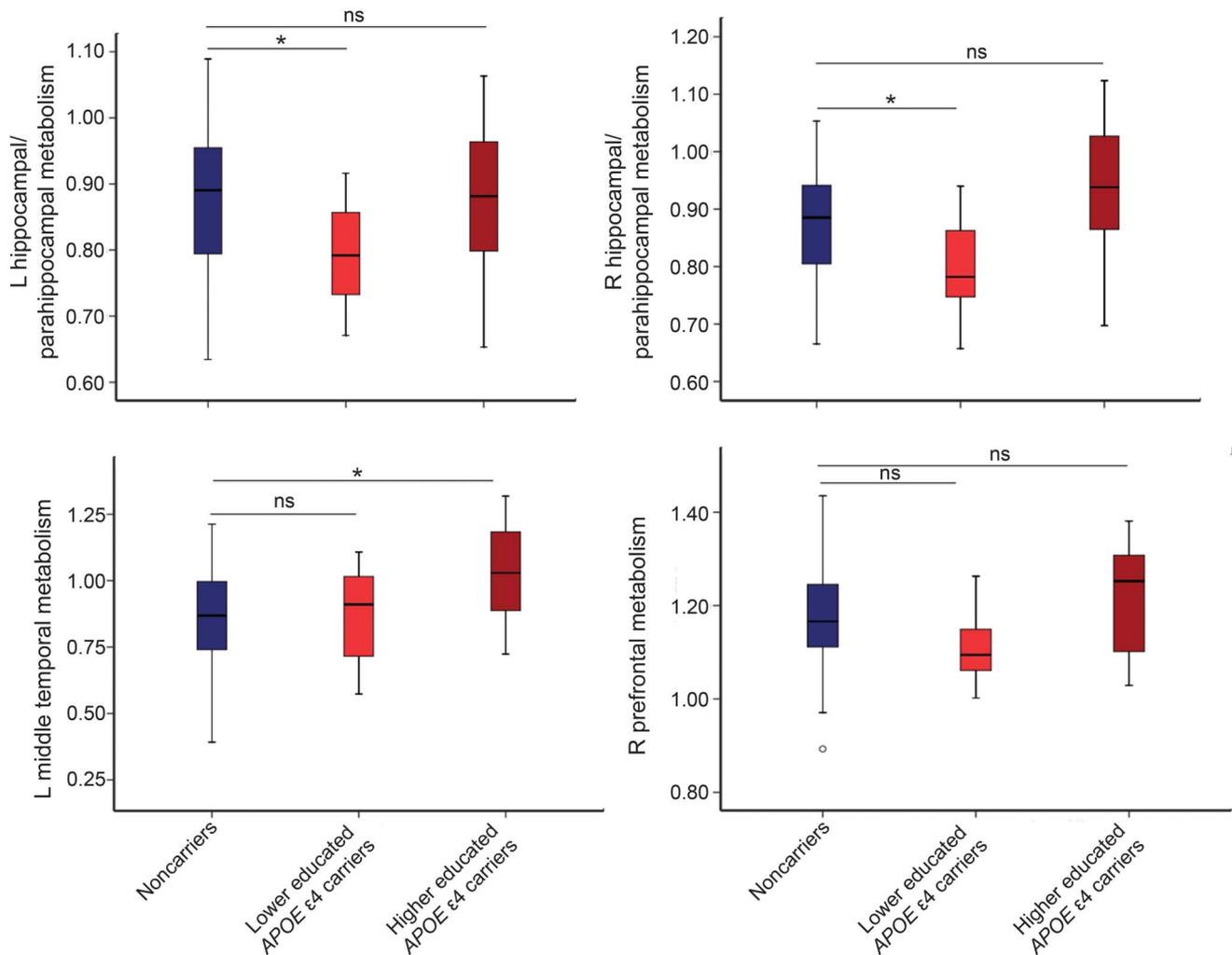
From left to right: noncarriers (in blue), lower educated *APOE* ε4 carriers (in light red), and higher educated *APOE* ε4 carriers (in red). ns = nonsignificant. *p < 0.05.

education was found in *APOE* ε4 carriers only. Effects of physical and cognitive activities restricted to *APOE* ε4 carriers have been found in previous studies considering cognitively normal older participants,[7,17,18] and may reflect the fact that *APOE* ε4 carriers are more vulnerable to lifestyle factors.[19,20]

In addition, our finding is consistent with previous neuroimaging studies supporting education (frequently combined with other variables such as occupation or IQ) as a protective factor for age[9] or AD-related[10,21,22] brain changes and extends the findings to cognitively normal *APOE* ε4 carriers. However, the mechanisms underlying the effect of education, and more generally the effect of lifestyle factors, remain unresolved. Growing evidence suggests that environmental factors may act through different pathways,[23,24] including direct effects on pathologic processes[22,25,26] (i.e., neuroprotective or brain maintenance mechanisms)[24] or involvement of compensatory mechanisms that would prevent

or delay cognitive changes related to pathology (cognitive reserve mechanisms).[27] Our complementary analyses provide insight into this question; however, definitive conclusions could not be drawn due to the small sample size. Thus, in medial temporal areas (and the prefrontal cortex, although not surviving correction for multiple comparisons), higher educated *APOE* ε4 carriers showed equivalent metabolism to noncarriers, while lower educated *APOE* ε4 carriers had reduced metabolism, which rather supports the former hypothesis. We could suggest that in these critical regions,[28–31] years of education help to maintain metabolism, counteracting *APOE* ε4-related metabolic decrease. By contrast, increased metabolism was found in higher educated *APOE* ε4 carriers compared to noncarriers in the middle temporal lobe, which would rather argue for brain or cognitive reserve mechanisms, or compensatory processes. Education-related FDG-PET metabolism increases in the temporal lobe have been reported in a previous study in cognitively normal older

participants[32] and were interpreted as a reflection of greater brain capacity to compensate for pathology. It is unlikely that the increased metabolism found in the present study reflects a compensation process for Aβ deposition, as we found our findings to be independent of Aβ deposition and we included young to old individuals, implying that a part of the sample would not be expected to show Aβ deposition. It might reflect a compensation response for another pathologic process since effects of APOE ε4 on the brain have also been described even in young age (see below), or a reserve mechanism that may help maintain cognition later in the disease progression. This would be consistent with a previous study showing almost no correlations between metabolism and Aβ in cognitively normal participants but strong negative correlations in participants with mild cognitive impairment (MCI).[33] One possible interpretation was that higher basal metabolism in MCI represented a reserve mechanism that increased the level of Aβ necessary for the clinical diagnosis of AD. However, this would need further investigation in future studies considering young-to-old APOE ε4 carriers and including different stages of the disease.

In addition to our results in APOE ε4 carriers, we also found decreased metabolism in the left hippocampus in higher educated noncarriers. Lower metabolism with higher education has also been reported previously in cognitively normal Aβ-positive participants.[10] Based on the cognitive reserve hypothesis, these results might reflect the fact that the same level of cognition could be achieved in higher educated individuals with lower metabolism than in lower educated individuals, owing to neural efficiency or neural compensation. While the reverse relationship between education and metabolism in APOE ε4 carriers and noncarriers suggests differential underlying mechanisms, this question would need additional investigation.

Overall, this and previous studies highlight the complexity of the mechanisms underlying lifestyle effects and the need to use multimodal neuroimaging approaches to understand the relationships between lifestyle factors, AD biomarkers, and compensatory mechanisms. In line with this, our results suggest that different processes can be highlighted in different brain regions (i.e., brain reserve or brain maintenance mechanisms) that may eventually result in maintained cognition. Indeed, this interpretation is reinforced by our complementary analysis showing a significant correlation between metabolism in frontal and temporal regions and episodic memory performances in APOE ε4 carriers.

We found these effects to be independent of age: the results were the same when using age as a confounding variable, as well as when assessing the interaction between APOE ε4 and years of education within 2 age groups. The fact that the interaction was also significant in the group of young individuals (<55 years), i.e., at an age where there is no Aβ deposition in the brain, also suggests that it was independent of Aβ deposition. Consistently, adding Aβ as a confounding variable did not modify our findings and the results were unchanged when only assessing the Aβ-negative individuals. Although it is thought that APOE ε4 genotype influence on AD is mainly driven by its effect on Aβ,[34,35] greater metabolic or structural abnormalities have also been detected in cognitively normal APOE ε4 carriers,[8] up to decades before brain Aβ levels become elevated.[28,29,36,37] This is consistent with growing evidence showing that APOE ε4 may act through both Aβ and non-Aβ pathways.[38]

Our study has limitations. First, the sample size is rather small, which may have prevented us from detecting more subtle effects. It is possible, for example, that an effect on gray matter volume would have been found in a larger sample. The use of a strong methodology on high-quality neuroimaging data from same center/scanner partly compensate for the decrease in the statistical power related to the size of the sample. In line with this, although our results were shown to be robust (after adjustment for several confounding factors and replication with vocabulary), they did not survive correction for multiple comparisons and the choice of the cluster extent threshold was arbitrary. Second, while our results were independent of age, years of education may be related to other variables that may impact positively on brain integrity later in life that were not measured in the present study. Also, even though our results were independent of sex, the effects of education in women and men would need further investigation in future studies, probably including larger sample sizes. Finally, although the most plausible explanation for our findings is an effect of education on the brain, the reverse causality, i.e., that persons with more efficient brain might seek higher education, cannot be excluded.

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