# Greater medial temporal hypometabolism and lower cortical amyloid burden in ApoE4-positive AD patients

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## Abstract

**Background**—ApoE4 has been associated with an increased risk of Alzheimer's disease (AD), amyloid deposition and hypometabolism. ApoE4 is less prevalent in non-amnestic AD variants suggesting a direct effect on the clinical phenotype. However, the impact of ApoE4 on amyloid burden and glucose metabolism across different clinical AD syndromes is not well understood. We aimed to assess the relationship between amyloid deposition, glucose metabolism and ApoE4 genotype in a clinically heterogeneous population of AD patients.

**Methods**—Fifty-two patients with probable AD (NIA-AA) underwent [11C]Pittsburgh compound B (PIB) and [18F]fluorodeoxyglucose (FDG) PET scans. All patients had positive PIB-PET scans. 23 were ApoE4+ (14 heterozygous, 9 homozygous) and 29 were ApoE4−. Groups consisted of language-variant AD, visual-variant AD, and AD patients with amnestic and dysexecutive deficits. 52 healthy controls were included for comparison. FDG and PIB uptake was compared between groups on a voxel-wise basis and in regions-of-interest.

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**Results—**Whilst PIB patterns were diffuse in both patient groups, ApoE4− patients showed higher PIB uptake than ApoE4+ patients across the cortex. Higher PIB uptake in ApoE4− patients was particularly significant in right lateral frontotemporal regions. In contrast, similar patterns of hypometabolism relative to controls were found in both patient groups, mainly involving lateral temporoparietal cortex, precuneus, posterior cingulate cortex, and middle frontal gyrus. Comparing patient groups, ApoE4+ subjects showed greater hypometabolism in bilateral medial temporal and right lateral temporal regions, and ApoE4− patients showed greater hypometabolism in cortical areas including supplementary motor cortex and superior frontal gyrus.

**Conclusions—**ApoE4+ AD patients showed lower global amyloid burden and greater medial temporal hypometabolism compared to matched ApoE4− patients. These findings suggest that ApoE4 may increase susceptibility to molecular pathology and modulate the anatomic pattern of neurodegeneration in AD.

## INTRODUCTION

Apolipoprotein E ε4 (ApoE4) has been associated with increased risk of Alzheimer's disease (AD), an earlier age of onset,[1] and greater memory impairments.[2] Whilst the effect of the ε4 allele on the risk and age of onset for AD is consistent across studies, there have been conflicting reports regarding the relationship between ApoE4 and pathological markers of AD in patients with dementia. Some autopsy and *in vivo* studies employing positron emission tomography (PET) with the amyloid-beta (Aβ)-specific tracer Pittsburgh Compound-B (PIB) have reported higher PIB uptake in ApoE4-carriers of AD,[3] whilst others have not found this effect,[4] or have shown the opposite pattern, with ApoE4-non carriers showing greater PIB uptake than ApoE4-carriers.[5] Recent findings from Aβ immunotherapy clinical trials further suggest differential treatment effects in ApoE4-positive and ApoE4-negative patients.[6] It is therefore important to gain a better understanding of the relationship between ApoE4 and amyloid deposition in AD patients.

In contrast, ApoE4 has been more consistently associated with greater abnormalities on neuroimaging across the AD continuum, with greater atrophy in medial temporal lobe regions reported in mild cognitive impairment (MCI) and AD patients, [7,8] and cognitively normal ApoE4-positive individuals reported to have greater hypometabolism in posterior cingulate, parietal, temporal, and prefrontal regions. [9] Whilst associations between ApoE and amyloid point towards a direct effect of ApoE on amyloid metabolism, including increased Aβ fibrillization and aggregation [10] and decreased Aβ clearance,[10,11] ApoE4 is also associated with hypometabolism in young individuals years prior to the age in which amyloid deposition is detected.[12] Altered activity and functional connectivity has also been reported in cognitively normal ApoE4-carriers that had no cerebral amyloid on PIB-PET.[13] These findings raise the possibility that functional and metabolic alterations in ApoE4-carriers are due, at least in part, to mechanisms that are independent of Aβ.

ApoE4 is also less common in non-amnestic variants of AD,[14] such as posterior cortical atrophy (PCA, predominant visual deficits), and logopenic variant of primary progressive aphasia (lvPPA, predominant language deficits) which are characterized by distinct patterns of neurodegeneration.[15] This suggests that the presence of the ApoE4 allele may have a direct effect on the clinico-anatomic phenotype of AD. It is therefore crucial to study the effects of ApoE4 on the brain not only in the typical variant of AD, but across different variants including non-amnestic early-onset variants since these could potentially be included in future clinical trials.

The current study aimed to assess the relationship between ApoE, amyloid deposition, and glucose metabolism in a clinically heterogeneous population of AD subjects. Whilst most studies have focused on healthy individuals and typical amnestic MCI and AD, using a clinically heterogeneous sample of AD patients allows us to examine the effects of ApoE4 in a more clinically and anatomically diverse population of AD patients which is important considering data suggesting that ApoE4 may influence the clinical phenotype. Apriori, we hypothesized that ApoE4+ AD patients would show greater hypometabolism in medial temporal lobe structures compared to non-carriers. Because of the inconsistent findings in the literature, we did not have an apriori hypothesis about the effect of ApoE4 on the distribution or burden of amyloid.

## METHODS

### Subjects

The study included 52 AD patients recruited at the University of California San Francisco (UCSF) Memory and Aging Center. All patients underwent a history and physical examination by a neurologist, a structured caregiver interview by a nurse, and a battery of neuropsychological tests.[16] All patients had at least one FDG-PET, PIB-PET and magnetic resonance imaging (MRI) scan. Scans were acquired between 2005 and 2012. All subjects fulfilled criteria for probable AD according to the National Institute on Aging-Alzheimer's Association (NIA-AA) criteria [17] and showed evidence of amyloid deposition on PIB-PET. Patients were excluded if they presented with core features of other dementias, (e.g. dementia with Lewy bodies), thereby reducing the likelihood of underlying co-pathologies that are associated with Aβ deposition. The AD group consisted of patients with different clinical variants: 12 (23%) had lvPPA, 13 (25%) had PCA, and 27 (52%) had predominant amnestic and dysexecutive deficits. The AD group was split according to ApoE4 status: 23 ApoE4-positive (ApoE4+, 9 of whom were ApoE4-homozygotes) and 29 ApoE4-negative (ApoE4−) patients. A group of 52 healthy controls was included for comparison. The majority of the control subjects (43/52) were recruited as part of the Berkeley Aging Cohort (BAC), with 9 subjects recruited at UCSF. All control subjects had amyloid-negative PIB-PET scans. It should be noted that the BAC eligibility criteria include a minimum age of 60, preventing a more accurate age-matching of controls to the young patients. Further eligibility criteria included normal performance on cognitive tests, absence of neurological or psychiatric illness and lack of major medical illnesses and medications that affect cognition. Informed consent was obtained from all subjects or their assigned surrogate decision-makers, and the study was approved by the University of California Berkeley, UCSF, and the Lawrence Berkeley National Laboratory (LBNL) institutional review boards for human research.

### PET image acquisition and preprocessing

All subjects underwent PET imaging with [11C] PIB and [18F] FDG at LBNL on a Siemens ECAT EXACT HR PET scanner in 3-dimensional acquisition mode. Tracer synthesis, PET acquisition, and preprocessing are described in detail in the supplementary methods. For PIB, voxel-wise distribution volume ratios (DVRs) were calculated using Logan graphical analysis [18] with the grey matter cerebellum time-activity curve used as a reference tissue input function. FDG-PET frames were summed and standard uptake volume ratios (SUVR) were calculated by normalizing the summed FDG image to mean activity in the pons for each subject,[19] PIB and FDG volumes were spatially normalized to Montreal Neurological Institute (MNI) space. All normalized images were smoothed with a 12-mm kernel. In a post-hoc analysis, we corrected PET data for atrophy by applying a 2-compartmental partial volume correction (see supplementary methods).

## MRI acquisition and processing

T1-weighted scans were collected on different MRI units, including two 1.5T, one 3T and one 4T unit (see supplementary methods for acquisition parameters). The proportions of subjects studied on each scanner were balanced across patient groups, though 94% of controls were studied on a single 1.5T scanner. Anatomical scans were processed using FreeSurfer version 4.5 (http://surfer.nmr.mgh.harvard.edu/fswiki) to generate subcortical parcellations used for defining subject-specific reference regions.

## Voxel-wise group comparisons

Voxel-wise comparisons of PIB DVR and FDG SUVR images were performed in SPM8 (Statistical Parametric Mapping,Version8; http://www.fil.ion.ucl.ac.uk/spm), using an analysis of covariance model that included group (controls, ApoE4+, ApoE4−) as the condition, and age, sex, and education as covariates. Between-patient group comparisons were additionally corrected for MMSE score. All voxel-wise comparisons were repeated using atrophy-corrected data. Resulting T-maps for control-patient comparisons were corrected for multiple comparisons using a family-wise error (FWE) correction at $p<0.05$ (extent threshold 0). Between-patient group comparisons are displayed at the most stringent threshold possible (FWE or uncorrected as applicable). Results are further shown as percent difference maps (−10% to 10% for all comparisons) to allow for a more consistent way of illustrating the data and to provide a full characterization of the FDG and PIB patterns. To account for any possible confounding effects of clinical presentation, we also repeated the voxel-wise comparison between patient groups correcting for clinical phenotype. We further conducted the analysis in the amnestic/ dysexecutive AD group only, which included a sufficiently large number of ApoE4+ and ApoE4− patients to assess differences within this syndrome. We further repeated the analysis correcting for scanner field strength to account for any possible confounding effects scanner strength may have on the data. Finally, associations between FDG and PIB in AD patients were assessed using ApoE as a continuous variable ($\varepsilon2\varepsilon3/\varepsilon3\varepsilon3$, $\varepsilon3\varepsilon4$, $\varepsilon4\varepsilon4$) correcting for age, sex, education and MMSE.

## ROI analysis

Seven ROIs in each hemisphere were created in MNI template space based on regions provided by the Automated Anatomical Labeling (AAL) atlas [20]: frontal (superior, middle, orbital, inferior, precentral), hippocampus, lateral temporal (superior, middle, inferior, temporal pole), posterior cingulate gyrus, precuneus, lateral parietal (superior and inferior), and occipital (superior, middle, inferior, lingual). FDG SUVR and PIB DVR values were extracted for each ROI, masking by the individual's grey matter images to exclude PET counts from white matter and cerebrospinal fluid. A global measure of PIB (PIB Index) was further assessed by extracting PIB DVR values from a large ROI consisting of frontal, lateral parietal, precuneus, lateral temporal, and cingulate cortex. FDG and PIB values were compared between patient groups (ApoE4+ AD vs. ApoE4− AD), adjusting for age, sex, education and MMSE.

## Statistical analysis

Statistical analyses were performed using STATA version 11.2 (STATA Corporation, College Station, TX, USA). Group differences in continuous demographic, neuropsychological and ROI data were examined using one-way analysis of variance (ANOVA) and Tukey post-hoc contrasts. Dichotomous variables were compared with Fisher's Exact test.

# RESULTS

## Subject characteristics

AD groups with different ApoE genotypes were well-matched for age, sex, education, MMSE score and age at onset (Table 1). Whilst the ApoE4− AD group included more lvPPA and PCA patients than the ApoE4+ AD group, this was not statistically significant (p=0.09). Both AD groups were significantly younger than the control group (p<0.0001) and had a lower MMSE score (p<0.0001). 12 (23%) of the control subjects were ApoE4+ (all heterozygotes).

## Neuropsychological profiles

Neuropsychological test batteries obtained within one year of PET were available for 22 ApoE4+ and 28 ApoE4− AD patients (Table 2). The mean interval between cognitive testing and PET was 91.6 days (SD 87.1 days). ApoE4− patients performed significantly worse on visuospatial testing (modified Rey Figure copying) and calculation compared with ApoE4+ patients. Whilst ApoE4+ patients performed slightly worse on memory tasks, this was not statistically significant. Further details on the neuropsychological profiles of each clinical syndrome are provided in Supplementary table 1.

## Voxel-wise group comparisons

### FDG patterns

Similar patterns of hypometabolism relative to controls were found in ApoE4+ and ApoE4− AD groups, mainly involving inferior parietal lobe, lateral temporal lobe, precuneus, posterior cingulate and dorsolateral prefrontal cortex (Figure 1). Comparing patient groups directly revealed greater hypometabolism in the ApoE4+ subjects in bilateral medial temporal and right lateral temporal regions, whereas ApoE4− patients showed greater hypometabolism in supplementary motor cortex and superior frontal gyrus (Figure 2). Results were unchanged after applying atrophy correction, although the spatial extent of between-group differences was more restricted (Supplementary Figure 1 and Supplementary Figure 2). Differences in FDG patterns between patient groups were also similar after correcting for phenotype (Supplementary Figure 3), and scanner field strength (data not shown), as well as within the amnestic/dysexecutive AD group (Supplementary Figure 4 and 5). Using ApoE as a continuous variable also produced similar results, with the ε4 copy number (ε2ε3/ε3ε3 > ε3ε4 > ε4ε4) associated with decreased metabolism in the medial temporal lobes, and higher metabolism in superior frontal and supplementary motor cortex (Supplementary Figure 6; T-maps do not survive multiple comparison correction).

### PIB patterns

PIB patterns were diffuse in both ApoE4+ and ApoE4− AD groups, involving most of the association neocortex (Figure 1). Overall, ApoE4− patients showed higher PIB binding compared with controls than ApoE4+ patients. The direct patient-group comparison (Figure 2) revealed higher PIB uptake in ApoE4− than in ApoE4+ patients in lateral frontotemporal regions (right>left). ApoE4+ patients showed some evidence of higher PIB binding in the medial temporal lobes, however, this was only significant at a very relaxed statistical threshold (p<0.05 uncorrected). Atrophy correction did not have a substantial impact on the results, although the statistical significance of the differences was greater in the atrophy-corrected than the non-atrophy-corrected comparisons (Supplementary Figure 1 and 2). Differences in PIB uptake between patient groups were also similar after correcting for phenotype (Supplementary Figure 3) or scanner field strength (data not shown) as well as within the amnestic/dysexecutive AD group (Supplementary Figure 4 and 5). Similar results were also obtained when using ApoE as a continuous variable, with the ε4 copy number (ε2ε3/ε3ε3 > ε3ε4 > ε4ε4) being negatively associated with PIB uptake across the cortex (Supplementary Figure 6; T-maps do not

survive multiple comparison correction, except for a small cluster (cluster size k=14) in the pars opercularis for the negative association (FWE p<0.05)).

### ROI analysis

FDG values were lower in both ApoE4+ and ApoE4− AD groups compared with controls in all 7 ROIs (p<0.0001; see Supplementary Table 2 for complete overview of FDG and PIB results). Comparing the AD groups directly revealed differences only in the hippocampus, with ApoE4+ patients showing less FDG uptake than ApoE4− patients.

PIB Index in the ApoE4− patients and ApoE4+ patients was higher than in controls, and was also higher in the ApoE4− than ApoE4+ patients. PIB in the 7 ROIs was higher in both AD groups compared with controls, except for the hippocampus, where only the ApoE4+ patients showed increased PIB in the right hemisphere. In the direct comparison between AD groups, ApoE4− patients showed higher PIB bilaterally in frontal, lateral temporal, lateral parietal, as well as in the right occipital lobe, posterior cingulate cortex and hippocampus.

## DISCUSSION

The current study aimed to investigate the effects of the ApoE4 genotype on amyloid deposition and glucose metabolism in a clinically heterogeneous population of AD subjects. We found that ApoE4-carriers showed a similar degree of temporoparietal hypometabolism and greater medial temporal hypometabolism in the presence of lower cortical amyloid burden than matched ApoE4-non carriers. These findings suggest that ApoE4 may increase susceptibility to molecular pathology and modulate the anatomic pattern of neurodegeneration in AD. Our findings add to a growing number of studies describing brain abnormalities that are associated with the ApoE4 allele but are not mediated by fibrillar Aβ deposition, suggesting that AD develops along distinct pathways in ApoE4-carriers and non-carriers.

Whilst the relationship between ApoE4 and greater amyloid burden are established in healthy controls and MCI,[4,21,22] data in AD patients are inconsistent. Autopsy and amyloid imaging studies have shown an association between ApoE4 and higher amyloid burden in AD patients, [3,23] whereas others have not found this relationship,[4,24] or have found the opposite pattern.[5] Reasons for the discrepant findings in AD dementia may include differences in subject characteristics, such as age-at-onset, disease severity, and clinical phenotypes, as well as methodological differences. Our data are consistent with a recent study that used an ROI approach to assess associations between ApoE4, FDG and PIB, reporting higher PIB uptake in ApoE4-negative AD patients in the frontal cortex in the presence of reduced metabolism in the occipital lobe.[5] Our study extends these findings by assessing differences in FDG and PIB across the brain (using voxel-wise comparisons), and by including the hippocampus in the ROI analysis. We also use partial volume corrected data to adjust for the effects of atrophy on the PET results. Subtle discrepancies in the findings between our study and Ossenkoeppele et al. (such as reduced metabolism in ApoE4-carriers in the occipital lobe) may result from differences in the clinical characteristics of patients included in each study. Further supportive evidence for amyloid-independent effects of ApoE4 comes from a recent study of healthy controls from the Alzheimer's Disease Neuroimaging Initiative (ADNI), showing a significant effect of ApoE4 on glucose metabolism that was not explained by the presence of fibrillar amyloid (measured using florbetapir-PET).[25] Therefore, accumulating evidence suggests that there are multiple pathways by which ApoE4 contributes to AD pathogenesis.

*In vitro* and *in vivo* studies in mice have shown that ApoE4 acts as a "pathological chaperone" [26] that induces Aβ aggregation and deposition into amyloid plaques. Suggested mechanisms by which the ApoE4 may affect amyloid deposition include increased Aβ fibrillization [27] and aggregation [28] as well as decreased Aβ clearance.[11] In addition, ApoE4 may preferentially direct Aβ to synapses, leading to greater synaptic loss in ε4-carriers.[29] These data suggest a direct and isoform-dependent interaction between ApoE and amyloid, contributing to AD pathogenesis.

On the other hand, ApoE has been shown to have many isoform-dependent effects on the brain that are independent of Aβ.[30] For example, ApoE is crucial for neuronal plasticity, [31] and is strongly involved in the transport of cholesterol.[32] Increased levels of ApoE are associated with neuronal growth and repair following injury in both the peripheral and central nervous system.[31] Impaired compensatory sprouting, neurite outgrowth, and reactive synaptogenesis have been shown in cell culture,[33] mouse models [31] and humans expressing ApoE4.[34] Density of dendritic spines has also been shown to be reduced in an age-dependent manner in the dentate gyrus of mice and humans carrying the ApoE4 allele.[35] A recent study in infants further underlines the crucial role of ApoE in brain development and functioning. In a large sample of 272 neonates it was shown that infants carrying the ε4-allele have lower temporal and greater parietal lobe volumes than ε4-non carriers.[36] ApoE also has an effect on mitochondrial function in cell cultures [37] and in human brains, with young ApoE4-carriers without Aβ showing reduced cytochrome oxidase activity compared to non-carriers.[38] Together, these data suggest that ApoE acts through Aβ-independent pathways, resulting in an increased vulnerability to metabolic impairment and neurodegeneration.

Whilst the relationship between ApoE and Aβ burden in AD requires further investigation, associations between ApoE4 and reduced glucose metabolism are consistent across studies. [39] The effects of ApoE isoforms on glucose metabolism also appear to be modulated by age of onset.[40] In our study, overall patterns of hypometabolism were similar in ApoE4-carriers and non-carriers compared with controls. However, subtle differences emerged in the direct between-patient comparisons. ApoE4-carriers showed greater hypometabolism in the hippocampus in both the voxel-wise and ROI analyses. Greater medial temporal lobe involvement in ApoE4-carriers was also found within the amnestic/dysexecutive AD group only. This is consistent with findings that ApoE4 is associated with an amnestic phenotype and greater volume loss in the hippocampi.[2,7] Greater regional vulnerability in ApoE4-carriers may contribute to early tangle formation in the transentorhinal cortex,[41] as well as loss of pyramidal cells in the hippocampal formation.[42] Higher levels of glucocorticoid receptors in the hippocampus have also been linked to increased vulnerability to stress [43] which may be heightened further in the presence of ApoE4. In contrast, ε4-non carriers showed a more cortical pattern of hypometabolism. This is in accordance with observations that focal early-onset variants of AD, such as PCA and lvPPA, have greater cortical involvement and tend to be ApoE4-negative.[14] Indeed, in the current study the ApoE4-negative group included relatively more non-amnestic variants (lvPPA, PCA) than the ApoE4-positive group, which may explain the cortical-predominant neurodegenerative pattern and the greater visuospatial deficits in the ε4-negative group. This finding is also consistent with a previous study that reported greater medial temporal lobe atrophy in ApoE4-carriers, and greater frontoparietal atrophy ApoE4-noncarriers with AD dementia.[2]

How can we reconcile the clear association between higher amyloid burden and ApoE4 in healthy individuals and MCI patients in nearly all studies, with our finding of greater amyloid burden in ApoE4-negative AD patients? The most likely explanation is that in cross-sectional studies of healthy controls and MCI patients (that include a mix of individuals with and without underlying AD pathology), ApoE4 represents a marker that

identifies those subjects with underlying AD. In contrast, our study included only patients with AD dementia and positive PIB-PET, allowing us to directly evaluate the effects of ApoE4 on amyloid burden and metabolism in a population in which everyone is very likely to have underlying AD pathophysiology. Furthermore, tying in a recently proposed biomarker cascade model of AD pathogenesis,[44] it is also possible that ApoE4-carriers have a shorter lag between changes in amyloid deposition and neurodegeneration. The increased vulnerability to the pathological effects of amyloid in the presence of ApoE4 may move the neurodegeneration curve closer to the amyloid curve. Therefore, in studies such as ours that include ε4-carriers and non-carriers that are matched for age and disease severity, the degree of neurodegeneration is similar, but the amount of amyloid is relatively smaller in ApoE4-carriers. However, further investigations are required to provide a better understanding of the processes underlying these seemingly discrepant findings.

Our study has limitations. Whilst including a clinically heterogeneous sample of AD patients was essential to our study aims, the inclusion of focal variants may have had an impact on the patterns of hypometabolism. However, reassuringly, correcting for phenotype in our analyses resulted in similar findings and patterns were also similar in the amnestic/dysexecutive AD group alone. Further studies including larger sample sizes are needed to further assess the effects of ApoE4 on glucose metabolism and amyloid separately in atypical AD syndromes.

Assessing these relationships in milder patients would also be important, however, the recruitment of patients with milder symptoms is often difficult owing to the atypical nature of the deficits seen in non-amnestic AD variants, which result in a delay in specialist referral and diagnosis.[45] Whilst not all voxel-wise comparisons survived rigorous FWE-correction, they are consistent with the data from the ROI analysis, and with our apriori hypotheses for FDG. ROI data were not corrected for multiple comparisons since it was limited to one pairwise comparison. Autopsy confirmation was only available in 3 patients (all AD), though our selection criteria were designed to maximize the likelihood of underlying AD pathology. Whilst PIB is a highly validated tracer, it is relatively novel and may have unknown limitations (e.g. ceiling effects, unknown binding interactions), and a direct effect of ApoE4 on PIB's binding affinity to amyloid cannot be excluded. A further point of ongoing debate is the potential confounding effects of atrophy on PIB data. Reassuringly our results were consistent with and without atrophy correction. MRI scans were acquired on different scanners. However, patient groups were matched for scanner type, and the use of structural imaging in this study was limited to definition of ROIs, spatial normalization and atrophy correction of PET data. Furthermore, repeating the analysis correcting for scanner field strength produced similar results. Finally, it is important to note that PIB binds only to fibrillar forms of Aβ, while soluble Aβ oligomers, which are considered the most neurotoxic of all amyloid species,[46] may significantly contribute to neurodegeneration in AD. Whilst using both PIB and FDG-PET allowed us to assess the effects of ApoE on patterns of amyloid deposition and metabolic impairment-related neurodegeneration, these were assessed independently. Our data do not allow conclusions about direct correlations between glucose metabolism and amyloid burden.

In summary, ApoE4-carriers showed a similar degree of hypometabolism in the presence of lower amyloid burden than matched ApoE4-noncarriers, suggesting greater metabolic vulnerability in ApoE4-carriers that is not explained by Aβ burden. Small reductions in metabolism in medial temporal regions in ApoE4-carriers correspond to the reported link between ApoE4 and an amnestic clinical phenotype in AD.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

## Acknowledgments

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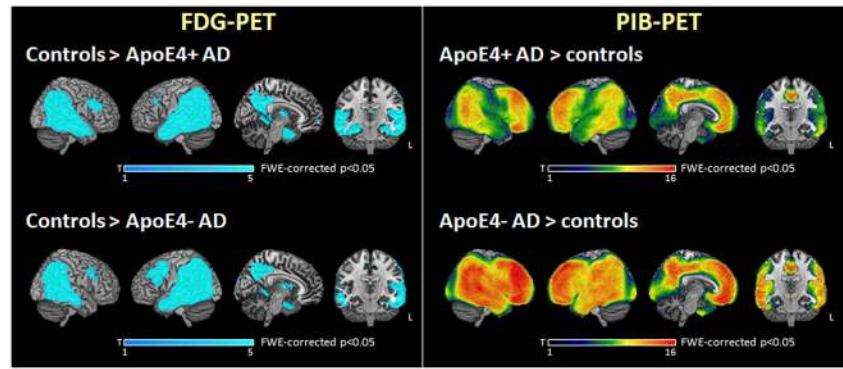
**Figure 1. Patterns of glucose metabolism (FDG-PET) and amyloid deposition (PIB-PET) in ApoE4+ and ApoE4− AD patients compared with controls**
Shown are T-maps after correction for multiple comparisons (FWE at p<0.05) rendered on the ch2 template brain. Blue in the FDG maps indicates significantly lower FDG uptake in the patient groups compared with controls, whereas warmer colors in the PIB maps indicate significantly greater PIB binding in the patient groups.
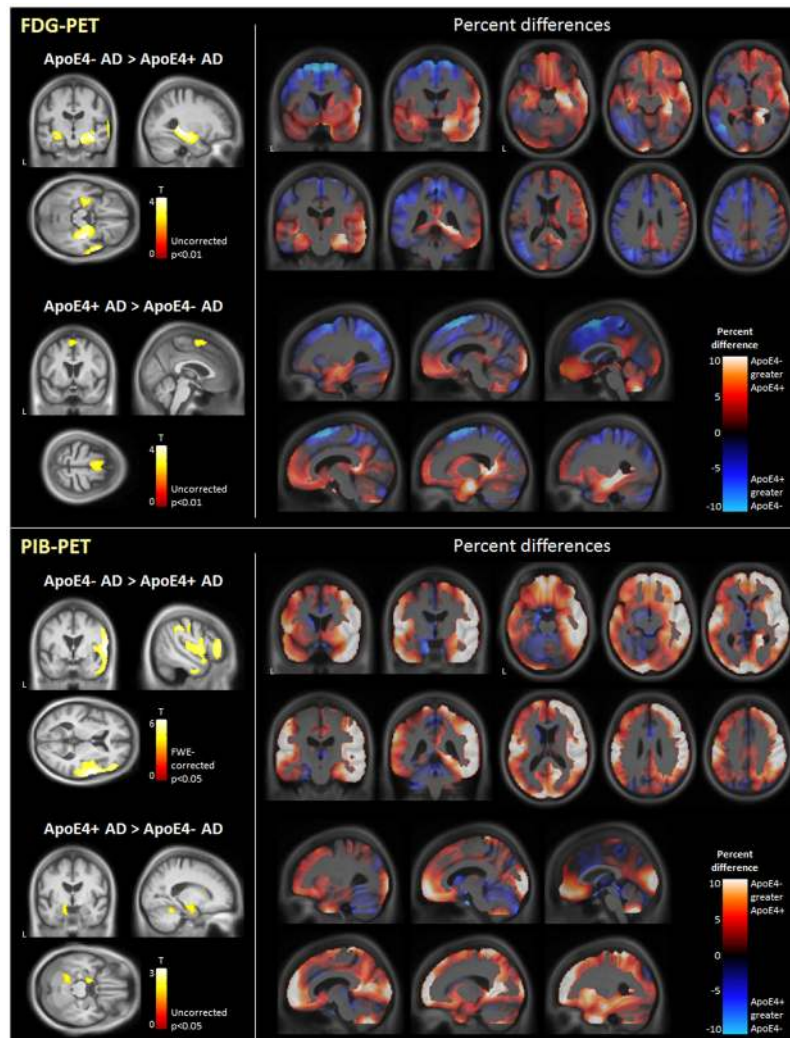
**Figure 2. Patterns of glucose metabolism (FDG-PET) and amyloid deposition (PIB-PET) in ApoE4+ and ApoE4− groups compared with each other**
The left panel shows statistical T-maps (uncorrected p<0.01 for FDG; FWE-corrected p<0.05 for PIB ApoE4− > ApoE4+, and uncorrected p<0.05 for PIB ApoE4+ > ApoE4−), whilst the right panel shows percent difference maps (−10% to 10%), with red indicating higher FDG/PIB uptake in the ApoE4− patients compared with ApoE4+, and blue indicating the reverse contrast. Images are shown in neurological convention.

**Table 1**

Subject demographics

| | Controls | ApoE4+ AD | ApoE4− AD | p[†] |
|---|---|---|---|---|
| **N** | 52 | 23 | 29 | - |
| **Age, years** | 72.3 (4.1) | 64.3 (8.9) | 62.7 (9.0) | 0.53 |
| **Gender, %male** | 42% | 52% | 59% | 0.78 |
| **Education, years** | 17.2 (1.8) | 17.3 (2.7) | 16.0 (2.8) | 0.12 |
| **MMSE (/30)** | 29.3 (1.0) | 21.3 (6.2) | 21.8 (6.1) | 0.81 |
| **Age at onset, years** | - | 59.7 (8.3) | 56.8 (9.0) | 0.24 |
| **N lvPPA / PCA / other AD** | - | 3 / 4 / 16 | 9 / 9 / 11 | 0.09 |
| **N ε3/ε4; ε4/ε4** | 12; 0 | 14; 9 | - | - |

Shown are means and standard deviations unless specified;

[†]for difference between ApoE AD groups;

MMSE – Mini-Mental State Examination; lvPPA – logopenic variant primary progressive aphasia; PCA – posterior cortical atrophy

**Table 2**

Neuropsychological test scores

| Neuropsychological test | ApoE4+ (N=22) | ApoE4− (N=28) | p[†] |
|---|---|---|---|
| **MMSE (/30)** | 21.6 (6.0) | 22.6 (4.9) | 0.34 |
| **Memory** | | | |
| CVLT total learning (/36) | 16.2 (5.7) | 16.1 (7.6) | 0.79 |
| CVLT 10-min recall (/9) | 1.6 (2.5) | 2.4 (2.5) | 0.27 |
| Modified Rey 10-min recall (/17) | 2.8 (3.6) | 4.0 (3.7) | 0.28 |
| **Language** | | | |
| Boston Naming Test (/15) | 10.7 (4.4) | 11.0 (3.4) | 0.79 |
| Syntax comprehension (/5) | 2.9 (1.4) | 2.9 (1.5) | 0.71 |
| Letter fluency (D words) | 8.4 (5.2) | 8.9 (3.8) | 0.78 |
| Category fluency (animals) | 9.7 (4.5) | 9.1 (4.3) | 0.66 |
| **Repetition and working memory** | | | |
| Sentence repetition (/5) | 3.1 (1.5) | 2.7 (1.3) | 0.33 |
| Digit span forward (/9) | 5.1 (1.1) | 4.8 (1.2) | 0.41 |
| Digit span backward (/8) | 3.4 (1.3) | 3.1 (1.4) | 0.67 |
| **Executive function** | | | |
| Modified Trails B time (120″) | 95.7 (33.5) | 92.0 (31.7) | 0.79 |
| Modified Trails B correct lines/min | 9.4 (10.6) | 8.8 (8.5) | 0.85 |
| Stroop interference no. correct | 18.5 (15.1) | 14.9 (11.6) | 0.18 |
| **Visuospatial** | | | |
| Modified Rey copy (/17) | 12.9 (4.2) | 9.3 (5.7) | **0.03** |
| VOSP number location (/10) | 6.9 (2.8) | 6.7 (3.1) | 0.73 |
| **Calculations** | | | |
| Arithmetics, written (/5) | 3.6 (1.2) | 2.8 (1.4) | **0.04** |
| **CATS** | | | |
| Face matching (/12) | 11.0 (1.4) | 10.3 (2.2) | 0.31 |
| Affect naming (/16) | 11.5 (2.2) | 12.0 (2.4) | 0.53 |

Shown are means and standard deviations; 2 subjects are not included due to the interval between cognitive assessment and PET scan being over 12 months.

[†]Difference between ApoE AD groups, adjusted for age, gender and education.

CVLT: California Verbal Learning Test; VOSP: Visual Object and Space Perception battery; CATS: Comprehensive Affect Testing System.

Missing data: Rey Figure: 1 ApoE4+, 1 ApoE4−; Boston Naming: 1 ApoE4+; Syntax: 2 ApoE4+, 1 ApoE4−; Letter and category fluency: 1 ApoE4−; Digit span forward: 14 ApoE4+; 12 ApoE4−; Digit span backward: 2 ApoE4−; Modified Trails: 4 ApoE4+, 8 ApoE4−; Stroop: 6 ApoE4+, 6 ApoE4−; VOSP Number location: 4 ApoE4+, 5 ApoE4−; Arithmetics: 1 ApoE4+; CATS face matching: 8 ApoE4+, 4 ApoE4−; CATS affect naming: 9 ApoE4+; 7 ApoE4−.