Title

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Abstract

Previous preclinical studies have suggested a close relationship between cerebrovascular disease (CVD) and Alzheimer's disease. However, a direct correlation between CVD and amyloid burden has not yet been shown in humans. If there is a relationship between CVD and amyloid burden, it is possible that the apolipoprotein E4 (*APOE4*) genotype may have an effect on this relationship because *APOE4* is a risk factor for the development of AD. We therefore evaluated the effects of *APOE4* on the relationship between white matter hyperintensities (WMH), a marker of CVD, and amyloid burden, measured by ^{11}C-Pittsburgh compound B (PiB) PET. We recruited 53 patients with subcortical vascular cognitive impairments, who had both WMH on MRI and amyloid deposition assessed by PiB PET. Twenty-two of these patients were *APOE4* carriers (41.5%). In the *APOE4* non-carriers, a significant positive correlation was shown between the volume of WMH and PiB retention ($\beta = 7.0 \ 10^{-3}$, $p = 0.034$) while no significant correlation was found in *APOE4* carriers ($\beta = -9.0 \times 10^{-3}$, $p = 0.085$). Statistical parametric mapping analyses in *APOE4* non-carriers showed that WMH were associated with PiB retention in the bilateral medial occipitotemporal gyrus, cuneus, and superior cerebellum. Our results suggested that WMH are correlated with amyloid burden especially in the posterior brain regions in *APOE4* non-carriers. However, this correlation was not observed in *APOE4* carriers, perhaps because in these subjects the influence of *APOE4* overrides the effect of CVD.

Keywords

Alzheimer's disease; amyloid burden; apolipoprotein E4; cerebrovascular disease

INTRODUCTION

Subcortical vascular cognitive impairment (SVCI) refers to cognitive impairments due to cerebrovascular disease (CVD), which consists of subcortical vascular dementia (SVaD) and subcortical vascular mild cognitive impairment (svMCI) [1]. Pathological studies, however, demonstrated that patients who had been clinically diagnosed with SVaD often proved to have comorbid Alzheimer's disease (AD) pathologies [2–4]. A study by our group using Pittsburgh compound-B (PiB) PET, a sensitive method to detect amyloid plaque burden during life [5], also showed that over 30% of SVaD patients turned out to be PiB-positive [6].

In epidemiologic studies, there is increasing evidence that CVD and AD dementia are strongly associated [7–10]. Some preclinical studies also suggest that CVD may directly induce amyloid burden [11]. Therefore, it has been suggested that CVD may accelerate the

development of AD [12]. There are two possible mechanisms that could explain the growing evidence linking CVD and AD dementia. The first is that CVD accelerates the deposition of brain amyloid, which leads to AD dementia. The second possible interpretation is that CVD produces brain damage, which would reduce cognitive reserve and thus make the subjects more susceptible to the effects of AD pathology. One recent study of human subjects was unable to demonstrate any direct correlation between CVD and amyloid burden [13]. This result would be most consistent with the second mechanism (described above) that CVD lowers cognitive reserve without having a direct effect on development of brain amyloid pathology. However, this previous study did not consider the effect of the apolipoprotein E ε4 (*APOE4*) genotype on the relationship between CVD and brain amyloid. The *APOE4* genotype is considered a major risk factor for AD and is thought to lower the age of onset for the development of AD and accelerate the aggregation of amyloid plaques [14]. Some studies also showed that *APOE4* is associated with CVD, although their results were inconsistent [15–18]. Thus, it is possible that the *APOE4* genotype might have an effect on the relationship between CVD and amyloid burden.

The current study aimed to examine the effects of *APOE4* on the relationship between CVD, which was quantified as white matter hyperintensities (WMH) on fluid-attenuated inversion recovery (FLAIR) MRI, and brain amyloid, which was measured by PiB PET imaging. We evaluated the relationship between WMH and amyloid burden in *APOE4* carriers and non-carriers, respectively. We hypothesized that there may be a correlation between the two pathologies affected by the *APOE4* genotype status.

MATERIALS AND METHODS

Participants

A total of 136 SVCI patients were consecutively recruited at Samsung Medical Center from September 2008 to August 2011. Patients with SVaD met the diagnostic criteria for vascular dementia as determined by the Diagnostic and Statistical Manual of Mental Disorders-Fourth Edition (DSM-IV). DSM-IV criteria include the presence of focal signs suggestive of CVD; we defined the presence of focal signs as at least two focal neurologic signs out of corticobular, corticospinal, extrapyramidal signs and gait abnormalities. All SVaD patients had a significant ischemia on their MRI scans, which was defined as a volume of WMH 15 cm^3. This cutoff value of 15 cm^3 was the smallest volume of WMH in patients who met grade 3 modified Fazekas ischemia criteria. A prior study suggested that WMH volume measurement might be more sensitive than visual scores [19]. Patients with svMCI were diagnosed using the Petersen criteria [20] with the following modifications: 1) there was subjective cognitive complaint by the patient or his/her caregiver; 2) normal Activity of Daily Living (ADL) score by clinically and ADL scale (Seoul Instrumental ADL score below seven, which is a modified version of Lawton's 1969 Instrumental ADL) [21, 22]; 3) the patient showed an objective memory decline below the 16th percentile on neuropsychological tests [1, 23, 24]; 4) not having dementia; and 5) presence of a subcortical vascular feature defined as both focal neurological symptom or sign and the significant ischemia on MRI, as in the SVaD. We excluded patients with other structural lesions on brain MRI such as territorial infarction, intracranial hemorrhage, traumatic brain

injury, hydrocephalus, or WMH associated with radiation, multiple sclerosis, or vasculitis. The number of patients with svMCI and SVaD were 59 (43.4%) and 77 (56.6%), respectively.

Patients with SVCI were classified as PiB-positive (PiB+) or PiB-negative (PiB−) if they had a global PiB retention ratio greater than or less than 1.5, respectively [6]. Among the 136 patients with SVCI, 53 (39.0%) were positive for PiB retention, while 83 (61.0%) were negative. Since our aim was to investigate the relationship between the two pathologies, we considered that subjects that have only one of the two pathologies may be inappropriate for our study goal. Therefore, we only included, from our SVCI cohort, the SVCI patients with PiB-positive scan. Among the 53 patients who were PiB+, 58.5% were *APOE4* non-carriers ($n = 31$: $\varepsilon2/\varepsilon3$, $n = 6$; $\varepsilon3/\varepsilon3$, $n = 25$), and 41.5% were *APOE4* carriers ($n = 22$: $\varepsilon3/\varepsilon4$, $n = 18$; $\varepsilon4/\varepsilon4$, $n = 4$).

All patients completed a clinical interview and neurological examination, blood tests, and *APOE* genotype as described previously [6], and MRI scans at Samsung Medical Center using the same scanner. All patients also completed a three-step diagnostic process. First, patients completed a medical interview conducted by an experienced neurologist, who obtained a medical history, a history of cognitive, behavioral, and functional impairments, and performed neurological examinations, including the Mini-Mental Status Exam (MMSE), Clinical Dementia Rating Sum of Boxes (CDR-SOB), and Geriatric Depression Scale (GDS). The interview also included items to assess patients' abilities to engage in activities of daily living. Second, the neuropsychology team performed a number of neuropsychological tests and conducted a clinical interview for cognitive, behavioral, and functional impairments using semi-structured questionnaires. The scales for Neuropsychiatric Inventory and Activities of Daily Living (ADL) scales were completed. The ADL scale used in this study was Seoul Instrumental ADL score, which is a modified version of Lawton's Instrumental ADL [21, 22]. Third, patients were diagnosed based on the results of all the diagnostic tests (neuropsychological reports, blood tests, and MRIs). Blood tests included a complete blood count, blood chemistry test, vitamin B_{12}/folate measure, syphilis serology, thyroid functioning tests, and *APOE* genotyping. We obtained a written consent from each patient and the Institutional Review Board of the Samsung Medical Center approved the study protocol.

Neuropsychological tests

All patients underwent neuropsychological testing using the Seoul Neuropsychological Screening Battery (SNSB) [25, 26]. This battery contains assessments of attention, language abilities, praxis, four elements of Gerstmann syndrome, visuospatial functioning, verbal and visual memory, and frontal/executive functioning. Among these subtests, the quantitatively scorable tests, including digit span (forward and backward), the Korean version of the Boston Naming Test (K-BNT) [27], the Rey-Osterrieth Complex Figure Test (RCFT; copying, immediate and 20-min delayed recall, and recognition), Seoul Verbal Learning Test (SVLT; three learning-free recall trials of 12 words, a 20-minute delayed recall trial for these 12 items, and a recognition test), phonemic and semantic Controlled Oral Word Association

Test (COWAT), and a Stroop Test (word and color reading of 112 items during a 2-min period) were used in current study.

MR imaging and analysis

T2, T1, three-dimensional (3D) FLAIR, and T2 fast field echo (FFE) images were acquired for all 53 subjects at Samsung Medical Center using the same 3.0 T MRI scanner (Philips 3.0T Achieva). The MRI scanning protocol was the same as described previously [24].

Measurement of regional WMH volume

We quantified WMH volume (in cm^3) on FLAIR images using an automated method as previously described [28]. First, we extracted the WMH candidate regions on FLAIR images applying classification method and morphological operation to T1-weighted images. Second, in order to extract WMH, a threshold method was applied to the FLAIR images within the WMH candidate regions. Even though the threshold value was selected considering the range of image intensities, segmented results could contain false positive or false negative regions depending on the extent of WMH. If the results contained an error, the threshold value was reselected through visual inspection by two raters, and they reached a consensus in the case of discrepancy. The rate of agreement between two neurologists was 92.3%.

[^{11}C] PiB-PET imaging

All patients completed a standardized [^{11}C] PiB-PET scan spanning the entire brain at Samsung Medical Center or Asan Medical Center using a Discovery STe PET/CT scanner (GE Medical Systems, Milwaukee, WI) in 3-dimensional scanning mode that examined 35 slices, each 4.25-mm thick. First, the ^{11}C-PiB was injected into an antecubital vein as a bolus with a mean dose of 420 MBq (range 259–550 MBq). Sixty minutes after the injection, a CT scan was performed for attenuation correction. Afterwards, the 30-minute emission static PET scan was then initiated [6].

Data analysis of [^{11}C] PiB-PET images

PiB PET images were co-registered to each individual's MRIs, which were normalized to a T1-weighted MRI template. Using these parameters, MRI co-registered PiB PET images were normalized to the MRI template. The quantitative regional values of PiB retention on the spatially normalized PiB images were obtained by an automated volume of interest (VOI) analysis tool using the automated anatomical labeling atlas. Data processing was performed using SPM version 8 (SPM8) through Matlab 6.5 (Mathworks, Natick, MA, USA).

To measure PiB retention, we used the cerebral cortical region to cerebellum uptake ratio which is identical to the standardized uptake value ratios (SUVRs). The cerebellum was used as a reference region as it did not show group differences. We selected 28 cortical VOIs from left as well as right hemispheres using the automated anatomical labeling atlas. The cerebral cortical VOIs which were chosen for this study consisted of the following areas: bilateral frontal (superior and middle frontal gyri, medial part of superior frontal gyrus, opercular part of inferior frontal gyrus, triangular part of inferior frontal gyrus,

supplementary motor area, orbital part of superior, middle, and inferior orbital frontal gyri, rectus and olfactory cortex), posterior cingulate gyri, parietal (superior and inferior parietal, supramarginal and angular gyri, and precuneus), lateral temporal (superior, middle and inferior temporal gyri, and heschl gyri), and occipital (superior, middle, and inferior occipital gyri, cuneus, calcarine fissure, and lingual and fusiform gyri). Regional cerebral cortical SUVRs were calculated by dividing each cortical VOI's SUV by the mean SUV of the cerebellar cortex (cerebellum crus1 and crus2). The global PiB retention ratio was calculated from the volume-weighted averages of the SUVRs of the bilateral cerebral cortical VOIs. We defined the PiB retention ratio as a continuous variable.

Statistical analysis

Comparisons of demographic and clinical data between *APOE4* non-carriers and carriers were conducted using Student's t test for normally distributed variables, and the Mann-Whitney U test for non-normally distributed variables. Categorical variables were evaluated using a χ^2 test. In order to examine the relationship between WMH and PiB retention ratio, multiple linear regression analyses were performed using WMH as an independent factor and the global PiB retention ratio as a dependent variable with adjustment for age and gender. Assumptions of residual about normality, homoscedasticity, and independence were confirmed. Statistical significance was set at $p < 0.05$. Statistical analyses were conducted using PASW Statistics 18 (SPSS Inc, Chicago, IL, USA) software.

In order to examine the relationship between WMH and PiB retention and to determine the regions where this relationship was significant, a voxel-based statistical analysis of the PiB images was performed using the Statistical Parametric Mapping program, version 8 (SPM8), and Matlab 6.5 for Windows (Math Works, Natick, MA, USA). An SPM regression analysis was performed without global normalization, since the ^{11}C-PiB PET images had been normalized to the cerebellar ROI PiB binding. Multivariate regression analysis was performed using WMH as a predictor and the PiB retention ratio at each voxel as a dependent variable after adjusting for age and gender. Red or yellow colored area showed the statistically significant region with increased global PiB retention as the volume of WMH increased with adjustment for age and gender. We defined statistical significance as $p < 0.001$ (uncorrected for multiple comparisons).

We generated group-specific gray matter mask using T1-weighted images in order to exclude non-gray matter areas from the PiB images. We used classification method and chose the threshold of 0.5 to binarize gray matter probability map for the mask. Results were overlaid to a T1 weighted MRI of a representative male individual template provided by SPM.

RESULTS

Baseline characteristics of the subjects

Demographic characteristics and imaging findings of the 53 patients are presented in Table 1. There were no differences in demographics or severity of cognitive impairment between

APOE4 non-carriers and carriers. There were also no differences in the median volume of WMH or mean global PiB SUVR between the two *APOE* groups.

Correlations between WMH and global PiB retention ratio in APOE4 non-carriers and carriers

In the whole PiB+cohort, there was no correlation between WMH volume and cortical PiB retention (unstandardized coefficient $\beta = 4.0 \times 10^{-3}$, SE ($\beta$) = 3.0×10^{-3}, $p = 0.175$).

In the *APOE4* non-carriers, a significant positive correlation was shown between the volume of WMH and cortical PiB retention ($\beta = 7.0 \times 10^{-3}$, SE($\beta$) = 3.0×10^{-3}, $p = 0.034$). However, no positive correlation was found in *APOE4* allele carriers ($\beta = -9.0 \times 10^{-3}$, SE ($\beta$) = 5.0×10^{-3}, $p = 0.085$) (Fig. 1).

To evaluate the effect modification of *APOE4* status and WMH volume on amyloid burden, multiple linear regressions were performed in all *APOE4* carriers and non-carriers ($n = 53$ for total *APOE4* carriers and non-carriers). We used age, gender, WMH, *APOE4* status, and the interaction terms (*APOE4* status*WMH volume) as independent variables, and PiB retention ratio as the dependent variable. There tended to be interactions between *APOE4* status and WMH volume ($p = 0.090$).

Regional correlation between WMH and cortical PiB retention in APOE4 non-carriers and carriers

In *APOE4* non-carriers, WMH volume was positively correlated with PiB retention in the bilateral medial occipitotemporal gyrus, cuneus, and the superior part of the cerebellum such as culmen, declive, anterior quadrangular lobule (uncorrected $p < 0.001$) (Fig. 2). However, after false discovery rate (FDR) correction, the statistical significance disappeared in these regions.

In *APOE4* carriers, there were no regions showing the significant correlation between WMH volumes and PiB retention ratio. However, WMH volumes tend to have a negative correlation with PiB retention ratio in the right dorsolateral frontal, precuneus, and bilateral parietotemporal areas (uncorrected $p < 0.01$) (Fig. 3).

DISCUSSION

Our major findings were as follows. First, there was a significant positive relationship between the volume of WMH and PiB retention in the *APOE4* non-carriers, whereas no significant analogous relationship was seen in *APOE4* carriers. Second, the brain regions where WMH correlated with PiB retention were in the temporal, occipital, and superior cerebellar regions. Our findings suggest that WMH is associated with amyloid burden, especially in the posterior brain regions of *APOE4* non-carriers with PiB (+) SVCI. These findings raise the possibility that *APOE4* interacts with the pathogenesis of amyloid deposition in the presence of CVD. Possible mechanisms are discussed below.

Our first major finding of a positive correlation between the volume of WMH and PiB retention ratio in *APOE4* non-carriers is consistent with many epidemiologic studies

demonstrating an association between CVD and AD pathology [7–9, 12, 29]. Furthermore, a recent preclinical study showed the direct relationship between ischemic lesion and amyloid burden [11]. A previous study also suggested that patients with stroke had increased PiB retention in the peri-infarct region [30]. In contrast, one PiB PET study, based on healthy subjects with normal cognition, showed there was no correlation between the two pathologies [13], but this study did not factor in the effect of the *APOE4* genotype. Indeed, in the present study, we found no correlation between WMH and amyloid burden in the carriers and non-carriers combined. Another reason for the discrepancy between previous findings and our current findings may be the difference in the subject population. Our study included MCI and dementia patients with greater amounts of WMH and brain amyloid in comparison with the previous asymptomatic community subjects [13] with lower amounts of WMH and brain amyloid. Our finding might be supported by a more recent study showing that baseline WMH was positively correlated with the progression of amyloid burden over 2 years [31]. The mechanisms underpinning the positive correlation between WMH and PiB retention remain unclear. However, it is possible that these two factors interact with each other (interactive hypothesis). One hypothesis is that CVD, reflected by WMH can block the clearance of amyloid via perivascular lymphatic drainage [31–33]. Alternatively, amyloid deposition in small or medium sized arterioles can lead to amyloid angiopathy, which may also result in severe WMH [34, 35]. However, since both AD and vascular pathologies usually occur in the elderly and share risk factors such as hypertension, diabetes, and hyperlipidemia, it is also possible that both pathologies can occur independently by chance [12, 29, 36].

Our second major finding was that WMH were associated with amyloid burden predominantly in the temporal, occipital and superior cerebellar regions, which are not typically affected by amyloid burden in AD [37]. This finding is similar to a recent report that amyloid deposition occurred predominantly in the occipital areas and cerebellum in patients with carotid stenosis [38]. Our finding is also consistent with another previous study showing that baseline WMH was associated with progression of amyloid burden in the parieto-occipital region [31]. The reason why WMH were correlated with amyloid burden in the posterior brain region in *APOE4* non-carriers remains unclear. We suggest that there are at least two possibilities to explain the relationship between WMH and amyloid: (1) the distribution corresponds to the posterior circulation, which is supplied by vertebrobasilar system; [39] or (2) it is related to the topography of cerebral amyloid angiopathy (CAA). The posterior circulation may be vulnerable to injury and dysfunction of the endothelium leading to blood-brain barrier (BBB) disruption [40]. For example, patients with hypertensive encephalopathy have vasculopathic changes predominantly in the posterior circulation areas. Furthermore, emerging evidence suggests that BBB disruption may contribute to the development of AD [33, 41–44], possibly through increased blockage of amyloid clearance. Therefore, it is possible that CVD may result in preferential BBB disruption in the posterior circulation, which may induce increased amyloid deposition in these areas. Alternatively, the association between WMH and amyloid burden might be related to CAA, which involves predominantly the occipital and temporal regions [34, 45, 46].

We found no correlation between WMH and PiB retention in *APOE4* carriers, similar to a previous report that did not account for *APOE4* [13]. Although animal studies have shown that *APOE4* is associated with enhanced amyloid-β aggregation [47, 48] and reduced amyloid clearance [14, 42, 49], resulting in amyloid-β deposition, the mechanism by which *APOE4* promotes earlier age of amyloid deposition in humans is not known. Amyloid imaging studies have repeatedly shown that age and *APOE4* status are the primary predictors of brain amyloid load. Therefore, we suggest that the powerful effects of *APOE4* on brain amyloid override the effects of CVD (WMH) on brain amyloid in *APOE4* positive subjects. Alternatively, it might be related to the explanation that SVCI patients with severe WMH have less amyloid burden than SVCI patients with moderate WMH because both WMH and amyloid burden causes cognitive impairments. Indeed, there was a trend displaying negative correlation between WMH and amyloid burdens in *APOE4* carriers.

There are some limitations to our study. First, we were unable to test the hypothesis of a causal relationship between ischemia and amyloid burden because this was a cross-sectional study. Longitudinal studies with serial MRI and PiB PET would be able to examine this issue. Second, all of the patients in this study had cognitive impairment, which may limit the generalizability of the results. However, since both CVD and amyloid pathology are related to cognitive impairment, our population is representative of an important clinical manifestation of these processes. Third, we were unable to differentiate the parenchymal amyloid from vascular amyloid using PiB-PET. However, in this study, there were no subjects who met the clinical criteria for CAA [50] or showed restricted lobar microbleeds. Finally, after corrections for multiple comparisons with FDR, significant associations in the SPM analysis disappeared. However, to reduce the chances of missing important associations during the early stage of analysis, we used a statistical significance level of 0.001 without correction for multiple comparisons.

Nevertheless, this study is noteworthy because it is the first human study demonstrating the correlation of severity of small vessel related ischemia and amyloid burden in *APOE4* non-carriers, especially in the posterior cortical regions. Further investigation on the interaction of CVD and amyloid deposition may provide clues to treatment or prevention strategies for dementia.

Acknowledgments

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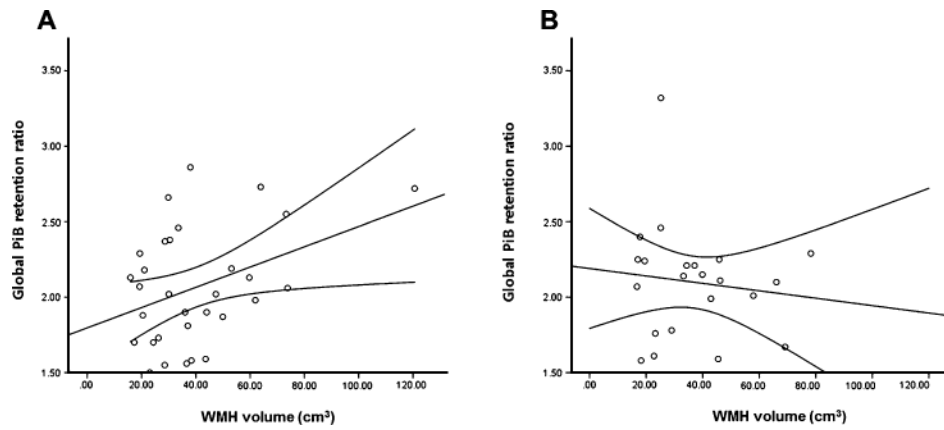
Fig. 1.
Scatter plot graph between the volume of white matter hyperintensities (WMH) (cm^3) and global PiB retention ratio. Multiple linear regression analyses were performed using WMH as an independent factor and the global PiB retention ratio as a dependent variable with adjustment for age and gender. A) Positive correlation with statistical significance was shown between WMH volumes and PiB retention areas in *APOE4* non-carrier ($\beta = 7.0 \times 10^{-3}$, SE($\beta$) = 3.0×10^{-3}, $p = 0.034$). B) Significant correlation was not shown between WMH volumes and PiB retention in *APOE4* carrier ($\beta = -9.0 \times 10^{-3}$, SE($\beta$) = 5.0×10^{-3}, $p = 0.085$).
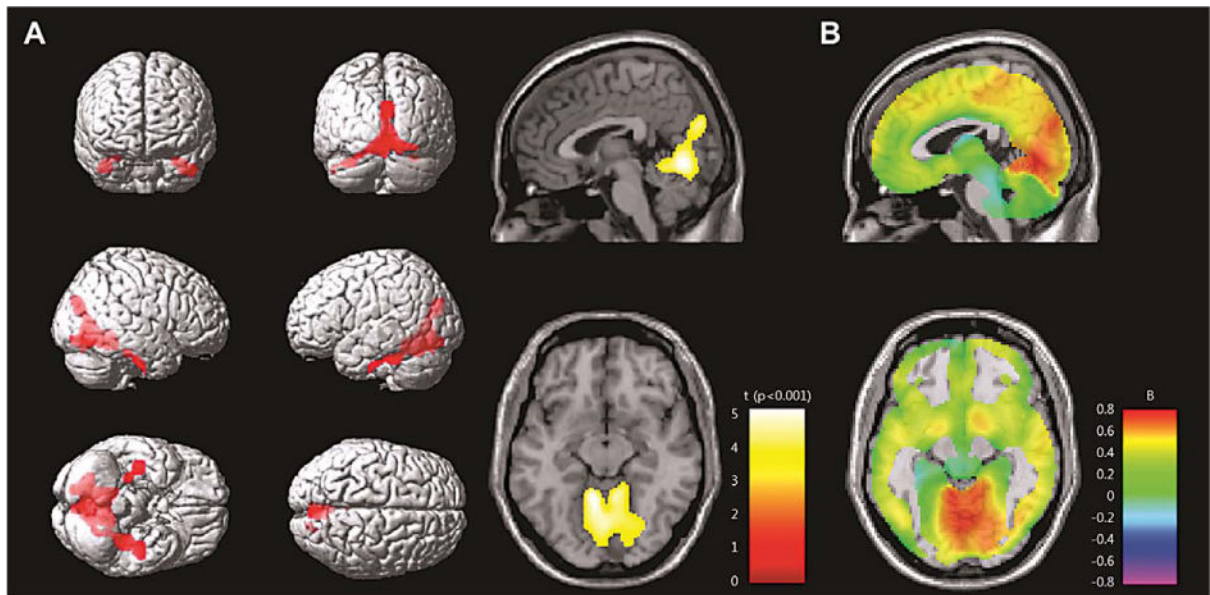
Fig. 2.
SPM multiple regression analysis of PiB retention in the *APOE4* non-carriers. A) t value map: The red or yellow colored regions represents the significant positive correlation between white matter hyperintensities volumes and PiB retention ratio with adjustment for age and gender (uncorrected *p* < 0.001). B) Beta map: Strength of associations is illustrated with color-labeled standardized beta-values.
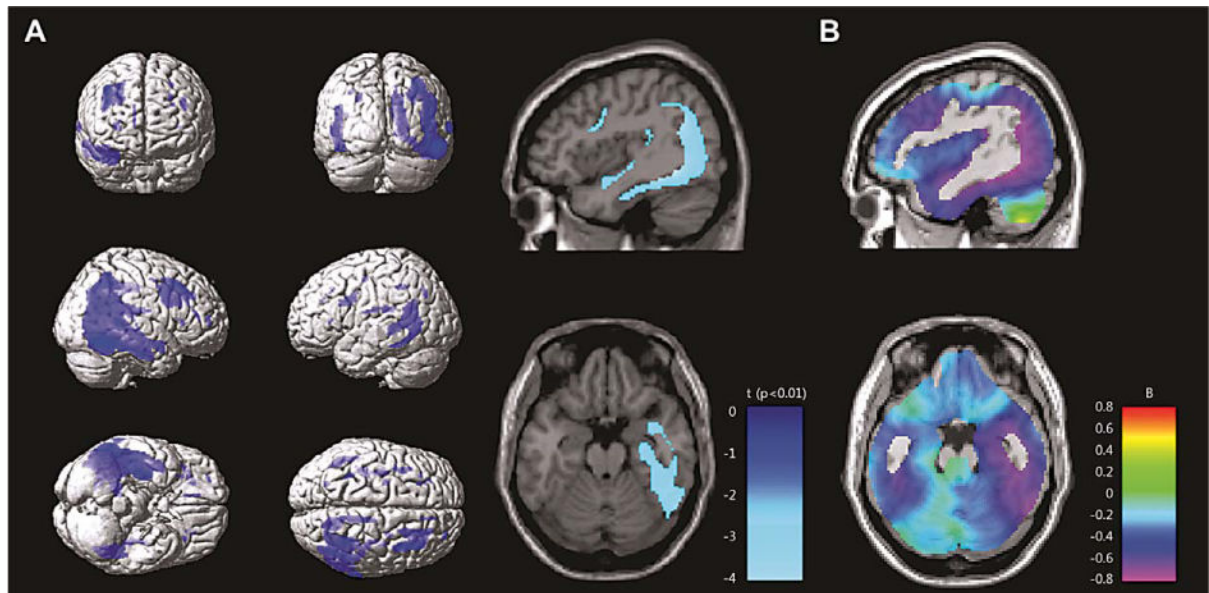
Fig. 3.
SPM multiple regression analysis of PiB retention in the *APOE4* carriers. There were no regions showing the significant correlation between WMH volumes and PiB retention ratio. A) t value map: The blue or sky blue colored regions represent the negative correlation between WMH and PiB retention ratio with adjustment for age and gender (uncorrected $p <$ 0.01). B) Beta map: Strength of associations is illustrated with color-labeled standardized beta-values.

Table 1

Demographic characteristics and imaging findings in study population

	APOE4 Non-carriers	*APOE4* Carriers	*p* value[‖]
Number	31	22	
Mild cognitive impairment[*]	11 (35.5%)	8 (36.4%)	>0.999
Age[†]	78.39 ± 5.14	76.41 ± 5.83	0.197
Male, N (%)[*]	13 (41.9%)	6 (27.3%)	0.420
Education (year)[†]	9.65 ± 6.21	9.91 ± 5.15	0.871
K-MMSE[†]	20.87 ± 5.78	22.59 ± 5.70	0.288
CDR SOB[‡]	3.50 (1.50–7.00)	3.50(1.50–6.00)	0.950
Hypertension[*]	17 (54.8%)	18 (81.8%)	0.080
Diabetes mellitus[*]	7 (22.6%)	6 (27.3%)	0.946
Dyslipidemia[*]	6 (19.4%)	7 (31.8%)	0.475
Coronary artery disease[§]	5 (16.1%)	3 (13.6%)	>0.999
Stroke history[§]	5 (16.1%)	3 (13.6%)	>0.999
WMH volume (cm^3)[‡]	36.02 (24.34–49.93)	33.77 (21.94–45.94)	0.626
Microbleed prevalence[*]	18(58.1%)	11 (50.0%)	0.561
Microbleed number[‡]	1.0 (0–4.0)	0.5 (0–4.0)	0.812
Global PiB retention ratio[†]	2.07 ± 0.38	2.10 ± 0.38	0.760

Data are presented as mean ± standard deviation for normally distributed and median (25th–75th percentile, interquartile range) for non-normally distributed variables.

[*] χ^2 test with Yates' continuity correction was used.

[†] Student's t test was used for normally distributed variables.

[‡] Mann-Whitney U test was used for non-normally distributed variables.

[§] Fischer exact test was used.

[‖] *p*-value for the comparison of the *APOE4* non-carrier group and *APOE4 carrier* group. K-MMSE, Korean version of the Mini-Mental State Examination; CDR SOB, Clinical Dementia Rating Sum of Box; WMH, white matter hyperintensities.