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Deep White Matter Lesions Are Associated with Early Recognition of Dementia in Alzheimer's Disease

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Abstract. Neuroimages of cerebral amyloid-β (Aβ) accumulation and small vessel disease (SVD) were examined in patients with various types of cognitive disorders using ^{11}C-labeled Pittsburgh Compound B-positron emission tomography (PiB-PET) and magnetic resonance imaging (MRI). The mean cortical standardized uptake value ratio (mcSUVR) was applied for a quantitative analysis of PiB-PET data. The severity of white matter lesions (WML) and enlarged perivascular spaces (EPVS) on MRI were assessed to evaluate complicating cerebral SVD using semiquantitative scales. In homozygous apolipoprotein E $\varepsilon 3/\varepsilon 3$ carriers, the incidence of more severe WML and EPVS was higher in PiB-positive than PiB-negative patients, indicating that WML and EPVS might be associated with enhanced Aβ accumulation. An association study between PiB-PET and MRI findings revealed that higher WML grades significantly correlate with lower mcSUVRs, especially in the frontal area, indicating that more severe ischemic MRI findings are associated with milder Aβ accumulation among patients with Alzheimer's disease. In these patients SVD may accelerate the occurrence of cognitive decline and facilitate early recognition of dementia.

Keywords: Alzheimer's disease, amyloid-β, dementia, Pittsburgh Compound B, positron emission tomography, white matter lesion

INTRODUCTION

Alzheimer's disease (AD) is a progressive neurodegenerative disorder resulting in cognitive impairment and behavioral disturbances. Brain neuropathological hallmarks of AD consist of senile plaques and neurofibrillary tangles [1, 2]. Senile plaques contain extracellularly deposited amyloid-β (Aβ) protein fibrils. ^{11}C-labeled Pittsburgh Compound B-positron emission tomography (PiB-PET) can detect cerebral Aβ protein *in vivo* and visualize the distribution of Aβ accumulation in brains with Aβ amyloidosis [3]. Previous autopsy studies have shown that PiB-PET images with increased PiB uptake correspond to regions with abundant senile plaques [1, 4]. Therefore, PiB-PET imaging is regarded a useful tool for diagnosing AD by detecting Aβ accumulation.

Previous studies have revealed that, in approximately 20% of cognitively normal elderly individuals, the levels of PiB uptake in the cerebral cortex

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are comparable to those of patients with AD [4, 5]. In addition, scores on neurocognitive batteries were not found to significantly vary among cognitively normal elderly individuals with different degrees of Aβ accumulation on PiB-PET [5, 6]. Although such individuals with cerebral Aβ accumulation, as indicated by PiB-PET, may be in the preclinical AD stage, it is possible that dementia-promoting factors other than Aβ pathology, such as cerebral small vessel disease (SVD), can cause early presentation of dementia in AD.

Several studies have reported that vascular risk factors (VRF), such as hypertension, hypercholesterolemia, and diabetes mellitus, are associated with an increased risk of developing AD [7–9], while others have shown that they are not associated with cerebral Aβ accumulation, seen on PiB-PET [10]. Moreover, VRF correlate with SVD [11]. Cerebral white matter lesions (WML) and enlarged perivascular spaces (EPVS) can be easily identified on cerebral magnetic resonance imaging (MRI) and constitute imaging biomarkers of SVD [12, 13]. Although WML and EPVS are characteristically associated with vascular dementia (VaD), their roles in AD pathogenesis have not been clarified.

Two independent studies have demonstrated the correlation between WML and Aβ accumulation [14, 15]. In contrast, a systematic review by Roseborough et al. indicated that most studies reported no statistically significant relationships between WML and Aβ accumulation [16]. Therefore, we aimed to investigate the association between cerebral Aβ accumulation and cerebral SVD in patients with cognitive impairments who underwent PiB-PET and MRI.

MATERIALS AND METHODS

Subjects

In total, 78 patients with clinically suspected AD (30 males, 48 females; age range 38–88 years, mean 69 years) who underwent PiB-PET imaging in the Department of Neurology, Gunma University Hospital, between October 2011 and March 2017, were enrolled in the present study, and their data were retrospectively analyzed. Among these 78 patients, 53 were clinically diagnosed with AD. All patients with AD fulfilled the diagnostic criteria of National Institute on Aging and Alzheimer's Association (NIA/AA) for probable AD dementia [17]. Written informed consent was obtained from all participants in the present study. The study protocol was approved by the institutional review board of the Ethics Committee of Gunma University Graduate School of Medicine.

Memory and cognitive functions were measured by the Mini-Mental State Examination (MMSE) [18], Frontal Assessment Battery (FAB) [19], and Montreal Cognitive Assessment (MoCA) [20, 21]. For depressive state assessment, the Geriatric Depression Scale (GDS) was used [22]. Functional abilities were assessed using the instrumental activities of daily living (IADL) scale [23].

VRF, such as hypertension, hypercholesterolemia, and diabetes mellitus, were identified using self-report, physical examination, and laboratory findings, and were dichotomized as present or absent, according to published guidelines.

MRI studies

All 78 patients with PiB-PET data also underwent cerebral MRI with T2-weighted and fluid attenuation inversion recovery (FLAIR) sequences. Data acquisition was conducted using three different MRI systems (General Electric 1.5T, Siemens 1.5T, and Siemens 3T).

Cerebral WML were analyzed using T2-weighted axial images. The severity of WML was assessed by a semiquantitative visual rating scale originally described by Fazekas et al. [24]. The severity of deep white matter hyperintensity (DWMH) was graded as G0 (absence), G1 (punctate foci), G2 (beginning confluence of foci), or G3 (large confluent areas) [24]. Similarly, periventricular hyperintensity (PVH) was graded as G0 (absence), G1 ("caps" or pencil-thin lining), G2 (smooth "halo"), or G3 (irregular PVH extending into the deep white matter) [24].

EPVS were assessed at the level of the hippocampus and basal ganglia/centrum semiovale and were defined as round (<3-mm diameter) or linear cerebrospinal fluid-isointense lesions exhibiting both hypointensity on T1-weighted imaging and hyperintensity on T2-weighted imaging or hypointensity on FLAIR imaging. The severity of EPVS was graded according to their number as follows: G0 (none), G1 (1–10), G2 (11–20), G3 (21–40), or G4 (over 40), and counted ipsilaterally on the side that was more severely affected [25].

Two board-certified neurologists (H.K. and S.T.), who were trained in neuroradiology, were blinded to clinical diagnosis and evaluated the T1-weighted, T2-weighted, and FLAIR images in a random order. In cases of disagreement, the grade of MRI lesions was ascertained by consensus. The inter-rater reliabilities were in good agreement, with weighted kappa values of 0.96 for DWMH, 0.98 for PVH, and 0.94 for EPVS assessments.

PET studies

Both PiB-PET and ^{18}F-labeled fluorodeoxyglucose PET (FDG-PET) studies were conducted in all 78 patients. ^{11}C-PiB and ^{18}F-FDG tracers were produced in our hospital cyclotron facility [3, 26, 27]. All PET studies were performed on a Discovery ST Elite scanner (General Electric Medical Systems, Milwaukee, WI). Emission scans were acquired in 3-dimensional mode without arterial blood sampling. After an intravenous injection of a mean dose of 555 MBq of ^{11}C-PiB, dynamic PET scanning was performed for 70 min. Images were loaded onto a Xeleris workstation (General Electric Medical Systems, Milwaukee, WI), where PiB-PET images were co-registered with the respective FDG-PET images [27]. The PiB-PET images were rated as positive or negative by inspection; if the uptake level in the cerebral cortex was more prominent than that in the white matter, they were rated as "positive."

The standardized uptake value ratio (SUVR) represents a quantitative measure of tracer uptake, which is normalized by the mean uptake in a reference region. Because PiB uptake in the cerebellar cortex is not different between patients with AD and healthy controls [4], it is a common strategy to select the cerebellar cortex as a reference region to evaluate the mean cortical SUVR (mcSUVR) on PiB-PET. Thus, since the cerebellar cortex is expected to have a lower fibrillar Aβ plaque burden than the cerebral cortex, it was used as a reference region to evaluate mcSUVR. Regions in the frontal cortex (FRC), parietal cortex (PAR), anterior cingulate gyrus (ANC), posterior cingulate gyrus (PCG), lateral temporal cortex (LTC), medial temporal cortex (MTC), and occipital cortex (OCC) were selected to calculate the mcSUVR of the respective areas [3, 28, 29]. Standard regions of interest (ROI) consisting of 1-cm diameter circles were manually placed on each cortical region of each PiB-PET image using the co-registered FDG-PET image. Representative arrangements of the standard ROIs on each region are shown in Figure 1A. A standardized single ROI was placed over three regions of the FRC, three of the PAR, one of the ANC, one of the PCG, three of the LTC, one of the MTC, and one of the OCC in the ipsilateral side [28, 30]. In order to compare the levels of regional PiB accumulation among subjects, four aggregated areas generated from the combination of multiple areas (Areas A, B, C, and D) were originally defined for further analysis, as shown in Figure 1B. Area A consisted of FRC, PAR, ANC, PCG, LTC, MTC, and OCC; area B consisted of FRC, PAR, ANC, and PCG; area C consisted of FRC and ANC; and area D consisted of PAR and PCG. The mcSUVRs of each aggregated area were calculated by averaging the SUVR values of all ROIs in each region.

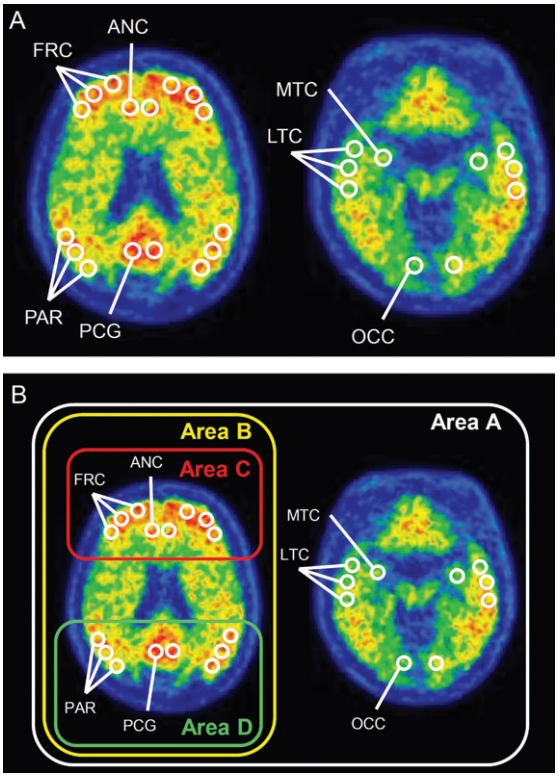


Fig. 1. Representative regions of interest (ROIs) and the aggregated areas defined on a ^{11}C-labeled Pittsburgh Compound B-positron emission tomography (PiB-PET) image of an Alzheimer's disease subject. A) Examples of the cortical ROIs examined in the present study (small white circles). B) Images showing how the four aggregated areas A, B, C, and D were defined, to evaluate regional PiB accumulation. ANC, anterior cingulate gyrus; FRC, frontal cortex; LTC, lateral temporal cortex; MTC, medial temporal cortex; OCC, occipital cortex; PAR, parietal cortex; PCG, posterior cingulate gyrus.

Genetic analysis of apolipoprotein E (APOE) genotypes

APOE genotypes were determined by the polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) technique, using purified genomic DNA samples from each individual, as described in a previous report [27, 31].

Statistical analysis

All statistical analyses were performed using SPSS 24 software (IBM Japan, Tokyo, Japan). Quantitative data are expressed as means ± standard deviations. Demographic and clinical parameters between the PiB-negative and PiB-positive groups were compared using an unpaired Student's *t*-test, and the categorical variables were compared using the χ^2-test. In case the number of the expected frequency was <5, a Yates' correction for continuity was applied. Mann–Whitney U test was used to compare the prevalence of each MRI grade of DWMH, PVH, and EPVS between PiB-negative and PiB-positive groups. The association between the mcSUVR and MRI grades was evaluated using Spearman's rank correlation coefficient. Multiple linear regression models were applied to explore the relationship between the mcSUVR and MRI grades independently of covariates. Weighted Cohen's Kappa was used to estimate inter-rater reliability on MRI assessment. The level of statistical significance was set as a p-value<0.05.

RESULTS

Demographic and clinical data

Demographic and clinical data of the PiB-negative and PiB-positive groups are summarized in Table 1. The participants who underwent imaging studies included 30 males and 48 females. According to inspectional assessment of the PiB-PET images, 67 patients (86%) exhibited a remarkable cortical PiB uptake and rated as PiB-positive, while the remaining 11 patients (14%) were PiB-negative. Among the 67 PiB-positive patients, 53 met the diagnostic

Table 1
Clinical characteristics of 78 patients who underwent PiB-PET

	PiB-negative (N = 11)	PiB-positive (N = 67)	*p*	Total (N = 78)
Age at examination (y)	61.7 ± 14.5	69.9 ± 9.5	<0.05*	68.7 ± 10.6
Male/Female	4/7	26/41	0.86 (χ^2)	30/48
Education level (y)	12.7 ± 3.2 (N = 10)	11.8 ± 2.1 (N = 59)	0.22	11.9 ± 2.3 (N = 69)
MMSE	25.7 ± 4.4 (N = 11)	19.3 ± 6.0 (N = 66)	<0.05*	20.2 ± 6.2 (N = 77)
FAB	13.2 ± 2.9 (N = 9)	9.1 ± 3.2 (N = 56)	<0.05*	9.6 ± 3.5 (N = 65)
MoCA	22.0 ± 5.1 (N = 8)	14.9 ± 4.8 (N = 50)	<0.05*	15.9 ± 5.4 (N = 58)
GDS	5.7 ± 5.5 (N = 7)	5.4 ± 3.6 (N = 45)	0.83	5.4 ± 3.8 (N = 52)
IADL	5.9 ± 2.5 (N = 8)	4.5 ± 2.1 (N = 39)	0.12	4.7 ± 2.2 (N = 47)
Hypertension	6 (N = 10)	38 (N = 61)	0.83 (χ^2)	44 (N = 71)
Hypercholesterolemia	5 (N = 10)	28 (N = 58)	0.81 (χ^2)	33 (N = 68)
Diabetes Mellitus	1 (N = 8)	17 (N = 56)	0.53 (χ^2)	18 (N = 64)
APOE genotypes				
2/2	0	2		2
3/3	10	28		38
3/4	1	22		23
4/4	0	5		5
Unknown	0	10		10

Qualitative data are expressed as the number, and quantitative data are expressed as the means ± standard deviations. The timing of evaluations for each item was the same when PiB-PET was performed. *indicates statistically significant results ($p < 0.05$). APOE, Apolipoprotein E; FAB, Frontal Assessment Battery; GDS, Geriatric Depression Scale; IADL, instrumental activities of daily living; MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment; PET, positron emission tomography; PiB, ^{11}C-labeled Pittsburgh Compound B.

criteria of NIA/AA for probable AD dementia, whereas the remaining 14 did not meet these criteria. These 14 patients were excluded from the diagnostic AD criteria because they exhibited extensive infarcts, prominent features of behavioral variant of frontotemporal dementia, prominent features of cerebral amyloid angiopathy, etc. At examination, PiB-negative and PiB-positive patients did not show significant differences in gender ratio and education level; however, PiB-positive patients were significantly older than PiB-negative ones ($p < 0.05$). In addition, no significant differences were found in the scores of GDS and IADL between groups; however, the scores for MMSE, FAB, and MoCA were significantly lower in the PiB-positive than in the PiB-negative patients ($p < 0.05$). No significant differences were found regarding VRF, including hypertension, hypercholesterolemia, and diabetes mellitus, between PiB-negative and PiB-positive patients (Table 1).

APOE genotype

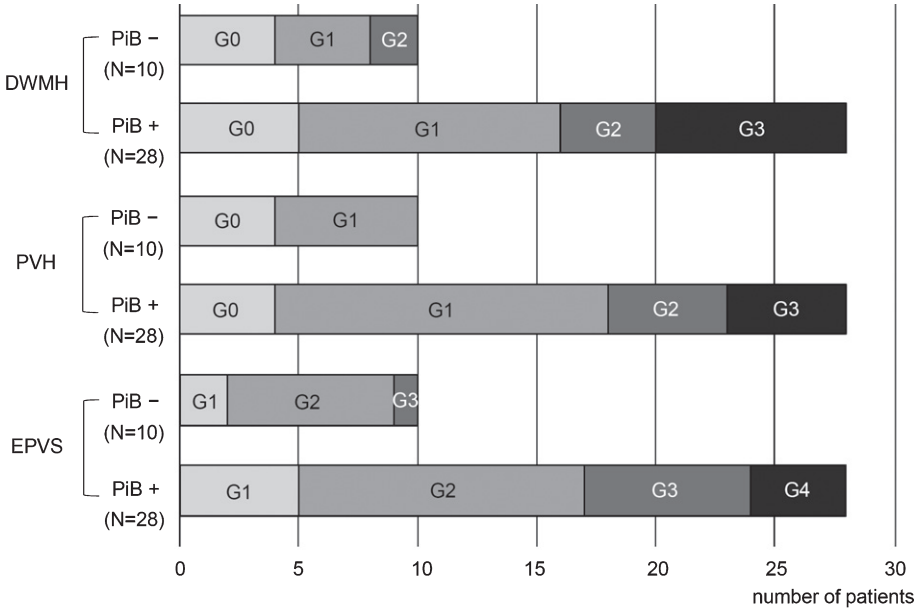
APOE genotypes were examined in the 11 PiB-negative patients and 57 of the 67 PiB-positive patients (Table 1). Among the 11 PiB-negative patients, 10 (91%) were homozygous for ε3/ε3, and 1 (9%) was heterozygous for ε3/ε4. Among the 57 PiB-positive patients, 2 (3%) were homozygous for ε2/ε2, 28 (49%) were homozygous for ε3/ε3, 22 (39%) were heterozygous for ε3/ε4, and 5 (9%) were homozygous for ε4/ε4. Homozygous APOE ε3/ε3 carriers were the most frequent in both the PiB-negative and PiB-positive groups. Homozygous APOE ε4/ε4 carriers were only found among PiB-positive patients. The frequency of patients carrying at least one APOE ε4 allele was significantly higher in PiB-positive (N = 27, 47%) than in PiB-negative patients (N = 1, 9%, $p = 0.04$; Table 1).

Cerebral WML on MRI in homozygous APOE ε3/ε3 carriers

In order to investigate the association between cerebral WML and PiB-PET findings, their severity in terms of DWMH and PVH, as well as EPVS, was examined in both the PiB-negative and PiB-positive groups (Fig. 2). Since the APOE ε4 allele is associated with an increased risk of developing AD [32] and potentially with increased occurrence of WML on MRI [33], we performed the MRI analysis only on patients with a uniform APOE genotype of homozygous ε3/ε3 alleles (N = 38). We did not find significant differences in age and gender ratio at examination between PiB-negative (N = 10) and PiB-positive (N = 28) patients (Table in Fig. 2) among the 38 homozygous APOE ε3/ε3 carriers. The frequency of each DWMH grade in the 10 PiB-negative patients was: G0 = 40% (N = 4), G1 = 40% (N = 4), G2 = 20% (N = 2), and G3 = 0% (N = 0); in the 28 PiB-positive patients the frequency was: G0 = 18% (N = 5), G1 = 39% (N = 11), G2 = 14% (N = 4), and G3 = 29% (N = 8) (Fig. 2, upper panel). The frequency of each PVH grade in the 10 PiB-negative patients was: G0 = 40% (N = 4), G1 = 60% (N = 6), G2 = 0% (N = 0), and G3 = 0% (N = 0); in the 28 PiB-positive patients the frequency was: G0 = 14% (N = 4), G1 = 50% (N = 14), G2 = 18% (N = 5), and G3 = 18% (N = 5) (Fig. 2, middle panel). Finally, the frequency of each EPVS grade in the 10 PiB-negative patients was: G0 = 0% (N = 0), G1 = 20% (N = 2), G2 = 70% (N = 7), G3 = 10% (N = 1), and G4 = 0% (N = 0); in the 28 PiB-positive patients the frequency was: G0 = 0% (N = 0), G1 = 18% (N = 5), G2 = 43% (N = 12), G3 = 25% (N = 7), and G4 = 14% (N = 4) (Fig. 2, lower panel). In homozygous APOE ε3/ε3 carriers, the percentage of patients with more severe MRI findings (i.e., grades ≥ G2 for DWMH and/or PVH; grades ≥ G3 for EPVS) was higher among PiB-positive than among PiB-negative patients (Fig. 2). The prevalence of each PVH grade was significantly different between PiB-negative and PiB-positive patients ($p < 0.05$).

Negative correlations between mcSUVR and MRI grades in patients with AD

To investigate the relationship between cerebral Aβ accumulation on PiB-PET and cerebral ischemic changes on MRI, we evaluated mcSUVRs in 30 AD patients with positive PiB-PET findings in relation to their MRI grades. Figure 3 shows the correlations between mcSUVRs and MRI grades of DWMH (Fig. 3, left column), PVH (Fig. 3, middle column), and EPVS (Fig. 3, right column). The mcSUVRs were evaluated for each aggregated area (Fig. 3: A, upper row; B, upper middle row; C, lower middle row; and D, lower row) and categorized as shown in Figure 1B. In the 30 patients with AD, the average mcSUVR of each aggregated area was: A, 1.95 ± 0.30; B, 2.03 ± 0.34; C, 2.07 ± 0.39; and D, 1.98 ± 0.36. In all aggregated areas, there was a negative correlation between mcSUVRs and the respective MRI grades. Higher



	PiB negative (N=10)	PiB positive (N=28)	*p*-value	Total (N=38)
Age at examination (years)	60.7 ± 14.7	66.7 ± 12.3	0.22	65.1 ± 13.0
Male/Female	4/6	15/13	0.71 (χ^2)	19/19

Fig. 2. Association of ^{11}C-labeled Pittsburgh Compound B-positron emission tomography (PiB-PET) findings and magnetic resonance imaging (MRI) grades for deep white matter hyperintensity (DWMH), periventricular hyperintensity (PVH), and enlarged perivascular spaces (EPVS) in homozygous apolipoprotein E (APOE) ε3/ε3 carriers. Demographic data of the 38 patients included in the analysis of this figure are shown in the table. PiB-negative and PiB-positive groups at examination did not show significant differences in age and gender ratio. In homozygous APOE ε3/ε3 carriers, the frequency of more severe MRI findings [i.e., grade (G)2 or G3 in DWMH and PVH, and G3 or G4 in EPVS] was higher in PiB-positive than in PiB-negative patients.

DWMH grades significantly correlated with lower mcSUVR in areas A ($r_s = -0.427$, $p = 0.019$), B ($r_s = -0.467$, $p = 0.009$), C ($r_s = -0.496$, $p = 0.005$), and D ($r_s = -0.432$, $p = 0.017$). Higher PVH grades significantly correlated with lower mcSUVR in areas B ($r_s = -0.374$, $p = 0.042$) and C ($r_s = -0.425$, $p = 0.019$). In contrast, while higher EPVS grades seemed to correlate with lower mcSUVR values, statistical significance was not reached in any of the aggregated areas. The effects of MRI grades regarding DWMH, PVH, or EPVS on mcSUVRs were tested using multiple linear regression models (Table 2) and including age at examination, hypertension, hypercholesterolemia, and diabetes mellitus. DWMH and PVH were associated with the mcSUVR in each aggregated area. EPVS was associated with the mcSUVR in aggregated area D, but not in areas A, B, and C. In addition, no significant correlations were observed between mcSUVRs and the presence of the assessed VRF, including hypertension, hypercholesterolemia, and diabetes mellitus.

DISCUSSION

The ε4 APOE allele is associated with Aβ accumulation in the brain

Several susceptibility genes have been previously identified for AD, among which the ε4 APOE allele has been confirmed as a major genetic risk for late-onset AD [32]. Among the three APOE alleles (ε2, ε3, and ε4), ε3 is the most frequent worldwide, and its prevalence is roughly estimated at 50–90% [34]. This allele was the most frequent (73%) among the 68 patients with available APOE genotypes included in the present study. Although the frequency of APOE alleles differs between populations, ε4 was reported to be present in about 50% of patients with late-onset

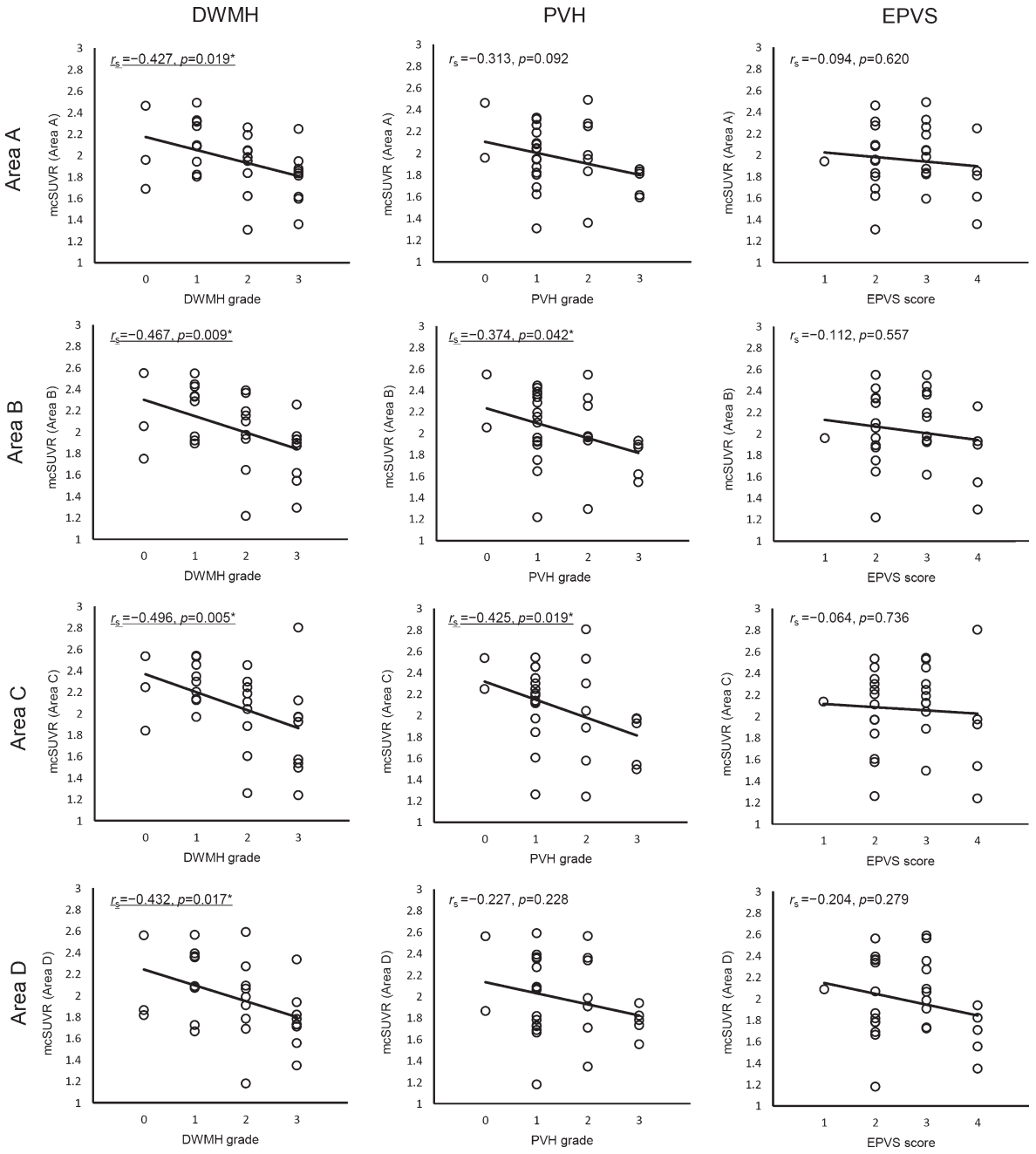


Fig. 3. Mean cortical standardized uptake value ratios (mcSUVRs) plotted against magnetic resonance imaging (MRI) grades among the 30 patients with Alzheimer's disease with positive ^{11}C-labeled Pittsburgh Compound B-positron emission tomography findings. The mcSUVRs were evaluated for each aggregated area: A (upper row), B (upper middle row), C (lower middle row), and D (lower row). Associations between mcSUVRs and MRI grades [deep white matter hyperintensity (DWMH): left column, periventricular hyperintensity (PVH): middle column, enlarged perivascular spaces (EPVS): right column] were evaluated by Spearman's rank correlation coefficient. Significant negative correlations were found between DWMH grades and mcSUVRs in areas A (upper row, left column), B (upper middle row, left column), C (lower middle row, left column), and D (lower row, left column), as well as between PVH grades and mcSUVRs in areas B (upper middle row, middle column) and C (lower middle row, middle column). The correlation coefficients underlined with an asterisk (*) are statistically significant ($p < 0.05$).

Table 2
Multivariable linear regression analyses in each aggregated area considering mcSUVR as the dependent variable

Area A	DWMH			PVH			EPVS		
	B	*B*'	*p*	*B*	*B*'	*p*	*B*	*B*'	*p*
MRI grades	**–0.16**	**–0.55**	**0.002***	**–0.18**	**–0.51**	**0.004***	**–0.12**	**–0.33**	**0.069**
Age	0.02	0.53	0.008*	0.01	0.46	0.018*	0.01	0.32	0.107
HT	–0.01	–0.02	0.932	0.08	0.14	0.445	0.11	0.19	0.348
HC	–0.26	–0.45	0.006*	–0.31	–0.54	0.002*	–0.35	–0.60	0.002*
DM	0.07	0.11	0.493	0.01	0.02	0.910	0.06	0.09	0.616
R^2		0.54			0.51			0.40	
AIC		–85.4			–83.8			–77.6	

Area B	DWMH			PVH			EPVS		
	B	*B*'	*p*	*B*	*B*'	*p*	*B*	*B*'	*p*
MRI grades	**–0.20**	**–0.57**	**0.002***	**–0.22**	**–0.54**	**0.003***	**–0.15**	**–0.35**	**0.064**
Age	0.02	0.48	0.019*	0.02	0.42	0.035*	0.01	0.26	0.196
HT	–0.00	0.00	0.998	0.11	0.16	0.391	0.15	0.21	0.309
HC	–0.28	–0.41	0.014*	–0.34	–0.50	0.004*	–0.38	–0.56	0.004*
DM	0.10	0.13	0.427	0.03	0.04	0.831	0.08	0.11	0.548
R^2		0.50			0.49			0.36	
AIC		–74.2			–73.4			–66.5	

Area C	DWMH			PVH			EPVS		
	B	*B*'	*p*	*B*	*B*'	*p*	*B*	*B*'	*p*
MRI grades	**–0.21**	**–0.54**	**0.002***	**–0.25**	**–0.55**	**0.001***	**–0.12**	**–0.26**	**0.157**
Age	0.02	0.46	0.020*	0.02	0.42	0.024*	0.01	0.24	0.238
HT	–0.00	–0.01	0.979	0.11	0.14	0.393	0.14	0.18	0.372
HC	–0.37	–0.49	0.003*	–0.43	–0.57	0.001*	–0.47	–0.62	0.002*
DM	0.21	0.25	0.123	0.13	0.15	0.320	0.19	0.22	0.222
R^2		0.54			0.56			0.38	
AIC		–69.2			–70.6			–60.1	

Area D	DWMH			PVH			EPVS		
	B	*B*'	*p*	*B*	*B*'	*p*	*B*	*B*'	*p*
MRI grades	**–0.19**	**–0.53**	**0.008***	**–0.17**	**–0.42**	**0.039***	**–0.18**	**–0.39**	**0.045***
Age	0.02	0.43	0.052	0.01	0.34	0.133	0.01	0.25	0.233
HT	–0.03	–0.04	0.864	0.08	0.11	0.603	0.13	0.18	0.415
HC	–0.21	–0.30	0.093	–0.27	–0.38	0.044*	–0.32	–0.45	0.022*
DM	–0.03	–0.03	0.847	–0.09	0.11	0.555	–0.04	–0.05	0.803
R^2		0.39			0.31			0.31	
AIC		–65.2			–61.8			–61.5	

The effects of MRI grades of DWMH, PVH, and EPVS on mcSUVR were tested using multiple linear regression models. *indicates statistically significant results ($p < 0.05$). Age, age at examination (years); AIC, Akaike's information criterion; *B*, partial regression coefficient; *B*', standardized regression coefficient; DM, diabetes mellitus; DWMH, deep white matter hyperintensity; EPVS, enlarged perivascular spaces; HC, hypercholesterolemia; HT, hypertension; mcSUVR, mean cortical standardized uptake value ratio; MRI, magnetic resonance imaging; PVH, periventricular hyperintensity; R^2, coefficient of determination.

AD and in 20–25% of healthy controls [35–37]. In the present study, the frequency of APOE ε4 carriers was 24% in the 136 chromosomes of patients with cognitive decline; however, ε4 frequency was significantly higher in chromosomes of PiB-positive patients (28%) than in those of PiB-negative patients (5%, $p = 0.04$). The difference in ε4 allele frequency between PiB-positive and PiB-negative individuals indicates that this allele may be associated with Aβ accumulation in the brain.

EPVS and WML are associated with cerebral Aβ accumulation

Cerebral WML are caused by chronic hypoperfusion and ischemic damage in the brain and are considered a surrogate marker of SVD [12]. Although such lesions have long been reported in VaD, some studies have demonstrated that they are more severe in patients with AD than in healthy controls [38–41]. Parietal WML seen in AD brains are also considered

to result from Wallerian degeneration as a consequence of AD pathology [42]. DWMH in the parietal lobe might also reflect the influence of AD pathology. In contrast, PVH does not extend to the parietal lobe in most cases and, thus, seems to reflect SVD rather than AD pathology. In the present study, WML severity, including DWMH and PVH, seemed to correlate with positive/negative PiB-PET findings in patients with homozygous APOE $\varepsilon 3/\varepsilon 3$. Specifically, PVH grades were significantly different between PiB-negative and PiB-positive groups. EPVS are also considered as a marker of SVD [13] and are more commonly found in elderly people [43–45] and in patients with hypertension [43, 45, 46], VaD [47], or lacunar stroke [43]. Although such WML have been reported as risk factors for AD [48], the association between EPVS and AD was heretofore unknown. In the present study, we found higher EPVS grades in PiB-positive than in PiB-negative patients, although the differences were not significant.

Cerebral Aβ accumulation in AD is more prominent in the frontal cortex than other regions

Currently, there are various protocols for defining ROIs for calculating the mcSUVR across brain regions. In the present study, several cortical ROIs (in the FRC, PAR, ANC, PCG, LTC, MTC, and OCC) were selected to assess the mcSUVR of the respective regions. It was previously reported that the prefrontal and lateral temporoparietal cortex, posterior cingulate, and precuneus exhibit higher PiB uptake values [3, 49–52]. In contrast, the occipital lobe, medial temporal lobe, and primary visual and sensorimotor cortical areas display lower uptake values [53]. In the present study, the average mcSUVR in the 30 patients with AD was highest in area C, followed by areas B, D, and A. Area C was located within the frontal lobes. Considering that PiB uptake signals were obtained only from the frontal lobes in area C, it reasonable that this area had the highest mcSUVR value among the areas analyzed.

Cerebral ischemic changes may facilitate recognition of dementia in AD

In the present study, we consistently found that higher MRI grades for DWMH, PVH, and EPVS correlated with lower mcSUVR values, indicating that more severe ischemic MRI findings are associated with milder cerebral Aβ accumulation on PiB-PET. It is possible that the reduced blood flow due to ischemic cerebral changes causes the reduced PiB uptake. A previous study investigated the association between WML and PiB uptake in cognitively normal elderly subjects and revealed a significant negative correlation between higher MRI grades for WML and lower PiB uptake in the white matter; however, no significant correlation was found between WML and PiB uptake in cerebral cortical areas [54].

MRI findings of DWMH, PVH, and EPVS are considered to be surrogate markers for SVD [12, 13]. However, they are thought to result from different pathological processes. EPVS are caused by the increased permeability of blood vessels [55] and are highly associated with aging and hypertension, but not hypercholesterolemia and diabetes mellitus [43, 45, 46, 56]. In contrast, DWMH and PVH arise from ischemic damages in the brain [12]. DWMH is associated with neuropathological changes caused by disruptions in nerve fibers, which result from ischemic changes, and are closely related to SVD [57], whereas PVH may result from blood brain barrier dysfunction or disruption in the ventricular ependymal lining, which leads to the subsequent leakage of cerebrospinal fluid into the periventricular white matter [58]. Therefore, DWMH is more associated with cerebral ischemic effects than PVH. When analyzed in the same aggregated area, DWMH, but not PVH, exhibited a higher negative correlation with mcSUVRs. Thus, DWMH, as more closely associated with cerebral ischemic changes than PVH, strongly correlates with cerebral Aβ accumulation.

Most previous studies investigating control or AD subjects have not reported any significant relationships between the degree of WML on MRI and cerebral Aβ accumulation on amyloid PET [16, 59, 60]. Two cohort studies reported statistically significant correlations between WML severity and cerebral Aβ accumulation, but the findings were contradictory. The first study by Zhou et al. reported a positive correlation between WML severity and Aβ accumulation in healthy elderly, MCI, and AD subjects [15], whereas the second study, based on the Alzheimer's Disease Neuroimaging Initiative (ADNI) database, by Provenzano et al., reported a negative correlation [14]. The results of the present study were similar to those of Provenzano et al. and suggested that, if SVD is severe in patients with AD, cognitive decline might be easily recognized, even if cerebral Aβ accumulation is relatively mild. The presence of Aβ accumulation on PiB-PET is considered to reflect AD pathology beginning in the preclinical stage. Thus, SVD in patients with AD pathology may accelerate

the occurrence of cognitive decline, and may facilitate early recognition of dementia in AD. A previous autopsy study on patients with AD revealed that the presence of cerebrovascular disease lowers the cognitive function of AD patients at an early stage of the Braak neurofibrillary tangle pathology [61]. The present study revealed that WML could lower the threshold of dementia recognition relative to the severity of AD pathology.

Although higher MRI grades for DWMH and PVH significantly correlated to lower mcSUVRs, no significant correlations were confirmed between mcSUVR and the presence of VRF, such as hypertension, hypercholesterolemia, and diabetes mellitus. Our results demonstrating a negative correlation between the severity of WML and Aβ accumulation were similar to those reported in the study by Provenzano et al. [14]. However, the authors of this study did not present detailed data, and the association between mcSUVR values and various VRF remained unclear. In the present study, we independently analyzed DWMH and PVH, as they resulted from different pathological processes. We found that PiB accumulation was particularly high in the frontal area (area C), with a negative correlation between DWMH grades and the mcSUVR value. Although previous studies have presented conflicting results on the correlation between WML and mcSUVR [14–16, 59, 60], we clearly confirmed a negative correlation in multiple of the defined aggregated areas. Given that additional cerebral ischemic damage in AD patients could accelerate cognitive decline, the degree of Aβ accumulation in patients with prominent WML may be milder at the time of PiB-PET examination.

Conclusion

The present study revealed that higher WML grades on MRI significantly correlate with lower mcSUVRs on PiB-PET among patients with AD. SVD in these patients may accelerate the occurrence of cognitive decline and, as such, facilitate early recognition of dementia.

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