

Regional Amyloid Accumulation and White Matter Integrity in Cognitively Normal Individuals

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Abstract.

Background: Recent studies have shown that amyloid- β ($A\beta$) burden influenced white matter (WM) integrity before the onset of dementia.

Objective: To assess whether the effects of $A\beta$ burden on WM integrity in cognitively normal (CN) individuals were regionally specific.

Methods: Our cohort consisted of 71 CNs from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database who underwent both AV45 amyloid-PET and diffusion tensor imaging. Standardized uptake value ratio (SUVR) was computed across four bilateral regions of interest (ROIs) corresponding to four stages of *in vivo* amyloid staging model (Amyloid stages I–IV). Linear regression models were conducted in entire CN group and between *APOE* $\epsilon 4$ carriers and non-carriers.

Results: Our results indicated that higher global $A\beta$ -SUVR was associated with higher mean diffusivity (MD) in the entire CN group ($p=0.023$), and with both higher MD ($p=0.015$) and lower fractional anisotropy (FA) ($p=0.026$) in *APOE* $\epsilon 4$ carriers. Subregion analysis showed that higher Amyloid stage I-II $A\beta$ -SUVRs were associated with higher MD (Stage-1: $p=0.030$; Stage-2: $p=0.016$) in the entire CN group, and with both higher MD (Stage-1: $p=0.004$; Stage-2: $p=0.010$) and lower FA (Stage-1: $p=0.022$; Stage-2: $p=0.014$) in *APOE* $\epsilon 4$ carriers. No associations were found in *APOE* $\epsilon 4$ non-carriers and in Amyloid stage III-IV ROIs.

Conclusions: Our results indicated that the effects of $A\beta$ burden on WM integrity in CNs might be regionally specific, particularly in Amyloid stage I-II ROIs, and modulated by *APOE* $\epsilon 4$ status.

Keywords: Amyloid PET, cognitively normal elders, diffusion tensor imaging, *in vivo* amyloid staging model, white matter integrity

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database (<http://adni.loni.usc.edu>). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in the analysis or writing of this report. A complete listing of ADNI investigators can be found at: http://adni.loni.usc.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf.

INTRODUCTION

Amyloid- β (A β) deposition in Alzheimer's disease (AD) can be detected by amyloid PET preceding the onset of cognitive decline by several decades [1, 2]. In addition, diffusion tensor imaging (DTI) studies demonstrate loss of white matter (WM) integrity in AD starting from the preclinical phase [3–7]. Increased mean diffusivity (MD) and decreased fractional anisotropy (FA) on DTI are regarded as biomarkers reflecting the loss of axons and myelin in the WM [8, 9]. Previous studies have investigated the relationships between A β deposition and WM integrity in the preclinical phase of AD. In a cohort of non-demented elders, two studies reported similar findings that subjects with lower cerebrospinal fluid (CSF) A β level showed higher MD and lower FA on DTI [10, 11].

Since the CSF levels of A β failed to show spatial difference of A β deposition, subsequent researches have examined the relationships between neuroimaging of A β deposition and WM integrity using amyloid PET [12, 13]. However, results have been inconsistent. For instance, one study found that an increase of neocortical A β burden assessed by amyloid PET was associated with an increase of MD in cognitive normal (CN) adults [12], whereas another study failed to find such an effect when assessing global A β level that are commonly used for classifying subjects into A β -positive or negative [13]. Based on these findings, we hypothesized that the associations between A β load and WM integrity in the asymptomatic phase of AD would be regionally specific.

Up to now, both autopsy [14–16] and PET [17] evidence have suggested that the ordering of regional A β deposition followed a relatively consistent pattern. The deposition of A β plaques starts from the basal temporal and medial frontal cortices, then spreads to the rest of associative neocortices, primary sensory-motor regions and medial temporal areas, and lastly the striatum. Grothe et al. defined these brain regions as Amyloid stages I, II, III, and IV, respectively [18]. Of the regions mentioned as showing loss of WM integrity in persons with A β accumulation, the neocortices are most relevant [12, 19], which are the first to develop A β pathology and correspond to Amyloid stages I and II [18].

In our study, we investigated the possible associations between A β deposition assessed by AV45 amyloid PET and WM microstructure assessed by DTI in cognitively normal (CN) individuals from the Alzheimer's Disease Neuroimaging Initiative

(ADNI) database. We assessed regional A β deposition in those brain regions, which are known to show increased susceptibility to A β pathology as defined by the *in vivo* established Amyloid staging model [18]. We hypothesized that the possible associations between high A β load and loss of WM integrity only existed in those neocortical regions corresponding to Amyloid stages I and II. Furthermore, we explored whether the possible associations were influenced by *APOE* genotypes.

MATERIALS AND METHODS

Study subjects and ADNI database

All participants recruited in our study were from the ADNI (ADNI-2 and ADNI-GO) cohort. The ADNI was a public-private partnership, which was led by principal investigator Michael W. Weiner, MD. Established in 2003, the ADNI aims to track the progression of mild cognitive impairment (MCI) and early AD using PET, magnetic resonance imaging (MRI), other biological markers, as well as neuropsychological and clinical assessment. Till now, the ADNI database has recruited over 1,500 individuals from no less than 50 sites across Canada and America. All participants provided written informed consent. More information can be found at <http://www.adni-info.org>. In our study, we restricted the present analyses to CN individuals whose data of AV45 amyloid-PET, DTI, WM hyperintensities (WMH) volume, and *APOE* genotype were available. Detailed descriptions of inclusion and exclusion criteria for CN individuals have been reported previously [20, 21]. Briefly, subjects were clinically categorized by ADNI centers as CN with a Mini-Mental State Examination (MMSE) scores of 24–30 where lower scores suggest more cognitive impairment (range, 0–30), and a Clinical Dementia Rating (CDR) score of 0 where lower scores indicate less cognitive impairment (range, 0–3). Subjects were assigned to the *APOE* ϵ 4 carriers when carrying at least one *APOE* ϵ 4 allele. Finally, our study recruited 71 CN individuals, including 23 *APOE* ϵ 4 carriers and 48 *APOE* ϵ 4 non-carriers at baseline (Table 1).

DTI data

DTI data was downloaded from the ADNI database. A detailed description of DTI image acquisition and processing can be found at <http://adni.loni.usc.edu/datasamples/mri/>. In brief, to

Table 1
Subject disposition and demographic characteristics

	CN	<i>APOE</i> ϵ 4 carriers	<i>APOE</i> ϵ 4 non-carriers	<i>p</i>
n	71	23	48	–
Age (y)	72.82 \pm 5.59	70.82 \pm 3.79	73.77 \pm 6.08	0.015
Gender (male/female)	31/40	8/15	23/25	0.430
Education (y)	16.37 \pm 2.70	15.57 \pm 2.64	16.75 \pm 2.66	0.085
WMH (cm ³)	8.94 \pm 14.72	11.24 \pm 22.81	7.83 \pm 8.69	0.495

Data are given as mean \pm standard deviation unless otherwise indicated. CN, cognitively normal individuals; *APOE*, Apolipoprotein. The differences in demographic characteristics between *APOE* ϵ 4 carriers and *APOE* ϵ 4 non-carriers were tested using t tests for continuous variables and Chi-squared tests for dichotomous variables. Bold text indicates $p < 0.05$.

segment WM regions of interest (ROIs), the FA image from the Johns Hopkins University (JHU) DTI atlas [22] was registered to each subject using mutual information based elastic registration algorithm which was described previously [23]. Then, the deformation was applied to the stereotaxic JHU “Eve” WM atlas labels using nearest neighbor interpolation to avoid intermixing of labels. This placed the atlas ROIs in the same coordinate space as our DTI maps. Finally, fifty-two WM ROIs were determined by the JHU white-matter tractography atlas. A list of the fifty-two WM ROIs can be found in Supplementary Table 1. For MD and FA on DTI are widely used biomarkers of WM integrity [8, 9], we computed average MD and FA values of the fifty-two WM ROIs for each individual as global MD and global FA, which represent the level of global WM microstructure.

AV45 amyloid-PET data

AV45 amyloid-PET data was also downloaded from the ADNI database. A detailed description of PET image acquisition and processing can be found at <http://adni.loni.usc.edu/datasamples/pet/>. In our study, we assessed global and regional AV45 amyloid-PET levels separately. Firstly, we averaged A β tracer uptake across four cortical regions (frontal, anterior/posterior cingulates, lateral parietal, lateral temporal) as global A β load that are commonly used for classifying subjects into A β -positive or negative [24]. And then we applied a recently proposed *in vivo* staging system of regional amyloid [18], that suggests A β deposition initiates in the basal temporal and medial frontal cortices (Amyloid stage I), then spreads to the rest of associative neocortices (Amyloid stage II), primary sensory-motor regions and medial temporal areas (Amyloid stage III), and lastly the striatum (Amyloid stage IV) [18]. We chose four brain regions corresponding to Amyloid stages I–IV as ROIs (shown in Fig. 1). We averaged A β tracer

uptake across brain regions that are included within each Amyloid stage ROI as stage-specific regional A β load. A list of brain regions that are included within each Amyloid stage ROI can be found in Supplementary Table 2. Finally, these mean values were normalized to the eroded WM reference region to obtain global and regional SUVR scores. The reason for choosing the eroded WM as a reference region was that reference regions containing subcortical eroded WM in cross-sectional studies appeared to be more accurate and sensitive when compared to cerebellum [25–29], and a recent study showed that WM A β tracer uptake may be an early predictor of WM microstructure [30].

Statistical analysis

We tested the differences in demographic characteristics between *APOE* ϵ 4 carriers and *APOE* ϵ 4 non-carriers using t tests for continuous variables and Chi-squared tests for dichotomous variables. We evaluated whether increased global or regional (i.e., four ROIs corresponding to Amyloid stages I–IV) AV45 amyloid-PET SUVRs were associated with the loss of WM integrity (i.e., global MD or global FA) using linear regression models, controlling for age, gender, educational level, and *APOE* ϵ 4 status (Model 1). To test whether the above associations were independent of WMH volume, we further included WMH volume as a covariate (Model 2). Considering that the accurate definition of a clinically meaningful cutoff value of SUVR in CN population remains unclear [31, 32] and using different cutoff values of SUVR may result in different findings [33], our study treated the level of A β deposition as a continuous variable. MD, FA, and AV45 amyloid-PET SUVR scores were log transformed prior to this analysis in order to approximately fit the normal distribution. Both the log-transformed independent and dependent variables in linear regression models were converted

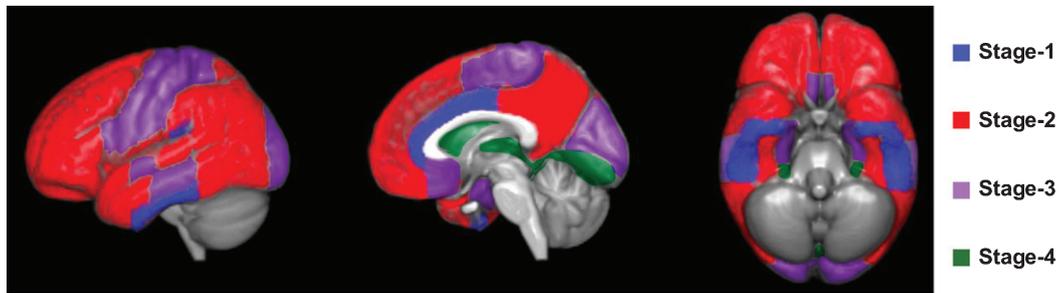


Fig. 1. Staging systems for amyloid-PET. Spatial mapping of amyloid stage-specific ROIs that were used to determine regional AV45 amyloid-PET uptake.

Table 2

	A β burden WM integrity	Global SUVR		Stage-1 SUVR		Stage-2 SUVR		Stage-3 SUVR		Stage-4 SUVR	
		MD	FA	MD	FA	MD	FA	MD	FA	MD	FA
Whole group (N = 71)											
Model 1	β coefficients	0.246	-0.204	0.234	-0.168	0.260	-0.226	0.129	-0.110	-0.092	0.147
	p	0.023	0.080	0.030	0.149	0.016	0.051	0.247	0.362	0.416	0.223
Model 2	β coefficients	0.201	-0.154	0.204	-0.136	0.211	-0.172	0.111	-0.089	-0.037	0.088
	p	0.045	0.154	0.039	0.204	0.035	0.110	0.28	0.417	0.726	0.433
APOE ϵ 4 carriers (N = 23)											
Model 1	β coefficients	0.416	-0.405	0.456	-0.395	0.438	-0.442	0.334	-0.308	-0.024	0.158
	p	0.015	0.026	0.004	0.022	0.010	0.014	0.057	0.099	0.902	0.437
Model 2	β coefficients	0.417	-0.406	0.462	-0.402	0.438	-0.440	0.334	-0.306	-0.029	0.171
	p	0.018	0.030	0.005	0.023	0.013	0.018	0.065	0.110	0.887	0.416
APOE ϵ 4 non-carriers (N = 48)											
Model 1	β coefficients	0.180	-0.118	0.127	-0.054	0.207	-0.152	0.094	-0.099	-0.098	0.106
	p	0.202	0.431	0.381	0.722	0.139	0.306	0.532	0.529	0.513	0.505
Model 2	β coefficients	0.095	-0.032	0.057	0.015	0.118	-0.063	0.028	-0.036	0.069	-0.056
	p	0.460	0.816	0.663	0.913	0.354	0.649	0.835	0.806	0.626	0.712

A β , amyloid- β ; APOE, Apolipoprotein; SUVR, standard uptake value ratio; WM, white matter. Model 1: p -values are based on linear regression models controlled for age, gender, education, and APOE ϵ 4 genotype. Model 2: p -values are based on linear regression models controlled for age, gender, education, APOE ϵ 4 genotype, and WMH volume. Bold text indicates $p < 0.05$.

into normalized z scores. Estimated effects of AV45 amyloid-PET SUVR on WM integrity are reported as β coefficients. Since all outcome variables were converted into normalized z scores, β coefficients refer to standardized effects. All statistical analyses were performed using a software program (R, version 3.6.0; The R Foundation). The criterion for statistical significance was $p < 0.05$. We did not correct for multiple comparisons because we expected to see differences only in ROIs affected at early Amyloid stages and included later-stage ROIs as control regions.

RESULTS

A total of 71 CN individuals were enrolled in our study, 40 of them were women and 31 of them were men. The mean age and education level of the entire CN cohort was 72.82 ± 5.59 and 16.37 ± 2.70 years, respectively (see Table 1 for sample character-

istics). Of the total, 48 had no APOE ϵ 4 allele, 22 had one, and 1 had two alleles. Subjects with at least one copy of the APOE ϵ 4 allele were categorized as APOE ϵ 4 carriers, and the others were classified into non-carriers. APOE ϵ 4 non-carriers with a mean age of 73.77 ± 6.08 years were older than carriers with a mean age of 70.82 ± 3.79 years ($p < 0.05$). No statistical differences in gender, education, and WMH volume were found between this two groups ($p > 0.05$).

In a first step, we tested the hypothesis that the increased A β deposition would be associated with the loss of WM integrity. We averaged A β tracer uptake across four cortical regions (frontal, anterior/posterior cingulates, lateral parietal, and lateral temporal) as global A β load that are commonly used for classifying subjects into A β -positive or negative [24]. Our results indicated that higher global AV45 amyloid-PET SUVR was associated with higher MD in the entire CN group ($p = 0.023$), and with both

higher MD ($p=0.015$) and lower FA ($p=0.026$) in *APOE* $\epsilon 4$ carriers when testing via linear regression models controlled for age, gender, education, and *APOE* $\epsilon 4$ genotype (see model 1 in Table 2). To test whether the above associations were independent of WMH volume, we further included WMH volume as a covariate and the results did not alter (see model 2 in Table 2).

We next tested whether the effects of A β deposition on WM integrity were regionally specific. For this, we assessed the AV45 amyloid-PET SUVR within four brain regions corresponding to Amyloid stages I–IV (Fig. 1) that recapitulate the spatial A β -spreading pattern from early-to-late-stage A β pathology [18]. The subregion analysis showed that the above positive findings only existed within regions corresponding to Amyloid stages I–II, which indicated that the higher regional AV45 amyloid-PET SUVRs in stage-1 and stage-2 ROIs were associated with higher MD (Stage-1: $p=0.030$; Stage-2: $p=0.016$) in the entire CN group, and with both higher MD (Stage-1: $p=0.004$;

Stage-2: $p=0.010$) and lower FA (Stage-1: $p=0.022$; Stage-2: $p=0.014$) in *APOE* $\epsilon 4$ carriers when controlling for age, gender, education, and *APOE* $\epsilon 4$ genotype (see model 1 in Table 2). When additionally controlling for WMH volume, these above associations remained fully consistent again (see model 2 in Table 2).

There were no significant associations in *APOE* $\epsilon 4$ non-carriers or in regions corresponding to Amyloid stages III–IV. The associations of global and regional A β deposition with MD and FA were shown in Figs. 2 and 3, respectively. Detailed β coefficients and p -values in total CN group including *APOE* $\epsilon 4$ carriers and *APOE* $\epsilon 4$ non-carriers were listed in Table 2.

DISCUSSION

Here, we adopted a hierarchical model of *in vivo* amyloid staging proposed by Grothe and colleagues [18] and applied it to explore possible associations of

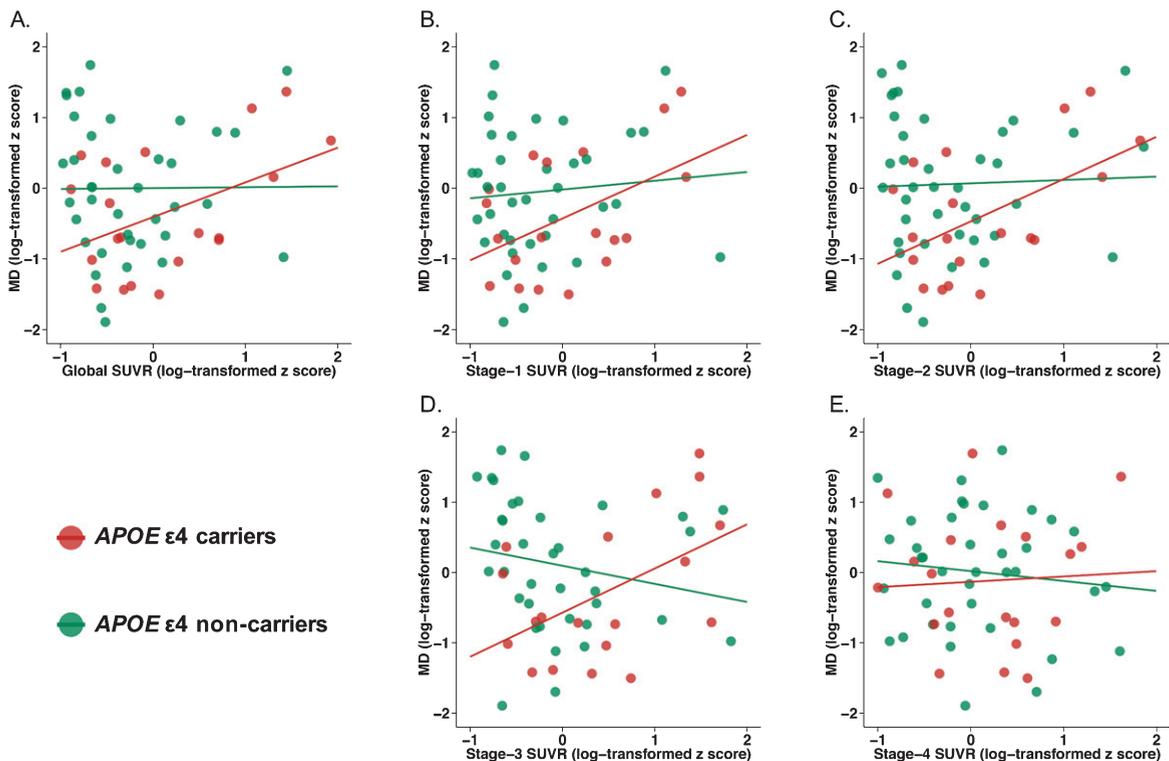


Fig. 2. Associations of global and regional A β burden with MD assessed by DTI. Global and regional (i.e., four ROIs corresponding to Amyloid stages I–IV) AV45 amyloid-PET SUVRs for each subject were plotted on the X axis, and MD for each subject assessed by DTI was plotted on the Y axis. AV45 amyloid-PET SUVR scores and MD were log transformed prior to this analysis in order to approximately fit the normal distribution. Both the log-transformed independent and dependent variables in linear regression models were converted into normalized z scores. The regression line is drawn separately for *APOE* $\epsilon 4$ carriers and *APOE* $\epsilon 4$ non-carriers for ease of comparison. A β , amyloid- β ; ROI, region of interest; SUVR, standard uptake value ratio.

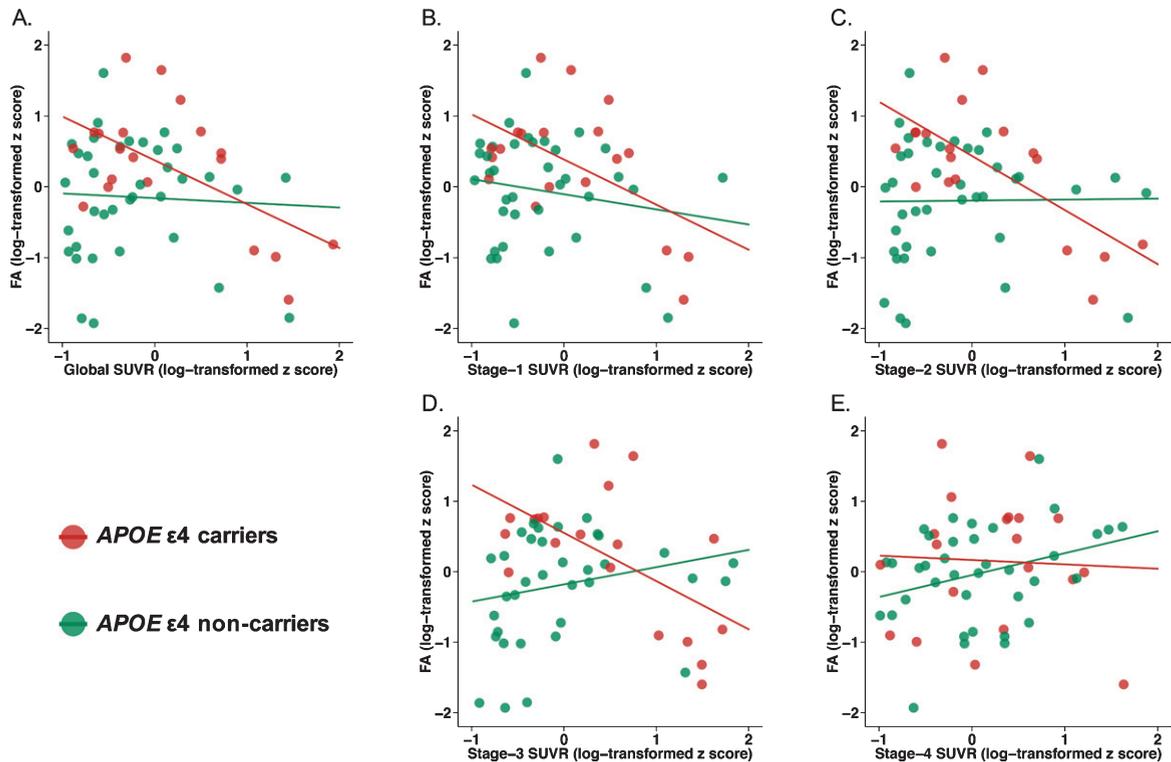


Fig. 3. Associations of global and regional A β burden with FA assessed by DTI. Global and regional (i.e., four ROIs corresponding to Amyloid stages I–IV) AV45 amyloid-PET SUVRs for each subject were plotted on the X axis, and FA for each subject assessed by DTI was plotted on the Y axis. AV45 amyloid-PET SUVR scores and FA were log transformed prior to this analysis in order to approximately fit the normal distribution. Both the log-transformed independent and dependent variables in linear regression models were converted into normalized z scores. The regression line is drawn separately for *APOE* ϵ 4 carriers and *APOE* ϵ 4 non-carriers for ease of comparison. A β , amyloid- β ; ROI, region of interest; SUVR, standard uptake value ratio.

A β deposition assessed by AV45 amyloid-PET with WM microstructure assessed by DTI in a cohort of CN individuals from the ADNI database. Our results indicated that: 1) the effects of A β load on WM integrity were regionally specific: basal temporal and medial frontal cortices, and the remaining associative neocortices (Amyloid stage I–II), which were the first to develop A β pathology, showed greater effects than primary sensory-motor regions and medial temporal areas, and the striatum (Amyloid stage III–IV), which only accrued A β plaques during symptomatic phase of AD; and 2) the aforementioned effects only existed in *APOE* ϵ 4 carriers, which indicated that the effects of A β load on WM integrity were modulated by *APOE* ϵ 4 status.

Our results provided supportive evidence for recent findings, which demonstrated that increased A β load was associated with the loss of WM integrity before the onset of dementia [10–13]. A preliminary study by Kalheim et al. compared subjects with low (A β positive) and normal CSF A β (A β negative) in a

cohort of non-demented elders consisting of MCI or subjective cognitive decline (SCD) and found that increased MD in subjects with low CSF A β [10]. Another study compared FA on DTI between subjects with higher A β load (A β positive, Amyloid PET SUVR > 1.69) and subjects with lower A β load (A β negative, Amyloid PET SUVR < 1.40) in a cohort of non-demented elders consisting of CN and MCI subjects. They found that higher A β burden was associated with lower FA in the presence of neurodegeneration (by hippocampal atrophy on MRI and hypometabolism on fluorodeoxyglucose PET) [13]. However, previous studies grouped participants into “A β positive” and “A β negative” based on CSF A β level or global A β deposition on amyloid PET [10, 13], which might fail to explore whether the effects of A β load on WM integrity showed regional differences. In addition, since conventionally defined “A β positive” usually corresponds to relatively late stages of A β pathology [31, 34], previous studies [10, 13] might fail to explore the potential associations

between early stages of A β pathology and WM integrity.

In our study, we treated the level of A β deposition as a continuous variable, considering that the accurate definition of a clinically meaningful cutoff value of SUVR in CN population remains unclear [31, 32] and using different cutoff values of SUVR might result in different findings [33]. Compared with previous studies, our study could detect the early stages of A β pathology below the threshold of conventionally defined "A β positive" by treating the level of A β load as a continuous variable.

We explored whether the potential associations between A β load and WM integrity showed regional differences by assessing regional AV45 amyloid-PET SUVR within four brain regions that recapitulate the spatial A β -spreading pattern from early-to-late-stage A β pathology [18]. Our results indicated that the higher regional AV45 amyloid-PET SUVRs in stage-1 and stage-2 ROIs were associated with higher MD in the entire CN group, and with both higher MD and lower FA in *APOE* ϵ 4 carriers. We selected later-stage ROIs (Amyloid stage III-IV) as control regions and did not find any associations between A β load and WM integrity in stage-3 and stage-4 ROIs. Although the p-value of stage-3 SUVR in the regression model regarding MD for the *APOE* ϵ 4 carriers subgroup approached the significance level ($p = 0.065$), we did not find any associations between stage-3 SUVR and MD/FA in the entire CN group and the association between stage-3 SUVR and MD in the *APOE* ϵ 4 carriers subgroup also failed to achieve the significant level ($p < 0.05$). These findings suggested that the associations between A β load and WM integrity in brain regions corresponding to Amyloid stages I-II were more significant than those in brain regions corresponding to Amyloid stages III-IV. The results were also in agreement with previous reports that A β deposition in neocortices, which correspond to Amyloid stages I-II, was associated with WM integrity in CN individuals [12, 19]. Since Amyloid stages I-II ROIs *in vivo* correspond to Thal amyloid phase 1 at autopsy [14], the similar findings in our study and previous studies [12, 19] suggested that the associations between A β accumulation and WM integrity starting from a very early stage and WM integrity assessed by DTI may be an early marker of A β pathology. We restricted the present analyses to CN individuals, whereas A β deposition in regions corresponding to Amyloid stages III-IV started from symptomatic phase of AD, which led to reduced variability in AV45 amyloid-PET levels in these brain regions and might

be the reason for the negative results. Additionally, the results of our study were required based on rather small sample size, which might attribute to the negative results as well. In our study, the p-value of stage-3 SUVR regarding MD approached the significance level. Future studies with larger sample size are needed to explore the effect of A β deposition in later-stage ROIs (Amyloid stage III-IV) on WM integrity in a mixed population consisting of CN, MCI and AD patients. The association between Stage-3 SUVR and MD/FA may be stronger on a larger cohort.

Our second major finding was that increasing A β load in early A β -associated brain regions, occurred only in *APOE* ϵ 4 carriers. We therefore hypothesized that the effect of A β load on WM integrity was modulated by *APOE* ϵ 4 status. This was consistent with the findings of recent studies exploring the effects of *APOE* ϵ 4 alleles on WM integrity. A study by Lee et al. found that *APOE* ϵ 4 carriers showed lower FA values in a cohort of SCD when compared with non-carriers [35]. Another study by Williams et al. [36] examined the interactive effects of vascular burden and *APOE* ϵ 4 status on WM integrity in CN elders and found *APOE* ϵ 4 carriers had greater decline in FA when compared to non-carriers. Given the small sample size of our study, the significant associations should be interpreted cautiously.

The above findings did not alter when additionally controlling for WMH volume, suggesting that the associations between A β load and WM integrity were independent of WMH volume. Recent studies have indicated that small vessel disease (SVD) may play an important role in the pathology of AD [37, 38], and SVD mainly affects subcortical WM. For WMH were often thought to be one of markers of SVD [39], we hypothesized that the effects of A β load on WM integrity might be independent of SVD. However, WMH are only one aspect of SVD, and many other manifestations are often detected in patients with SVD (e.g., cerebral microbleeds and lacunar cerebral infarction). Future studies are needed to determine whether the relationships between A β load and WM integrity are mediated by SVD.

Limitations

The present study has some limitations. Firstly, the sample size of the study was rather small, which may reduce the testing efficiency of whole and subgroup analyses to some extent. Secondly, majority participants in our study were relatively old (mean age: 72.82 years). Previous study indicated that middle-

aged adults may be an optimal target for early intervention. However, it remains unclear whether A β deposition is associated with WM integrity in middle-aged adults. Thirdly, as a cross-sectional study, we did not detect longitudinal associations between A β load and WM integrity. Finally, the p values in our study were just on the significant edge and the associations may be stronger on a larger cohort. There is a need to conduct a follow-up study with larger sample size and broader age range in the future.

Conclusions

In summary, the main finding of our current study was that increased A β load in basal temporal and medial frontal cortices, and the remaining associative neocortices (Amyloid stage I-II) might be associated with the loss of WM integrity in absence of cognitive impairment. The effects were more obvious with the presence of *APOE* ϵ 4 alleles.

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Authors' disclosures available online (<https://www.j-alz.com/manuscript-disclosures/19-1350r1>).

SUPPLEMENTARY MATERIAL

The supplementary material is available in the electronic version of this article: <https://dx.doi.org/10.3233/JAD-191350>.

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