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Influence of hypertension on brain amyloid deposition and Alzheimer's disease signature neurodegeneration

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ABSTRACT

This study aimed to investigate the relationship of hypertension with beta-amyloid (Aβ) and neurodegeneration biomarkers of Alzheimer's disease (AD) and the modulating effect of apolipoprotein E-ε4 (APOE4). In total, 259 cognitively normal (CN) and 79 AD dementia older adults received clinical assessments including the evaluation for the presence of hypertension, [^{11}C]-Pittsburgh-compound-B—positron emission tomography, magnetic resonance imaging, and APOE genotyping. We used a clinical stage-specific approach, separately focusing on CN and AD dementia stages. For the CN group, individuals with hypertension showed reduced AD signature cortical thickness compared with those without hypertension. Subsequent subgroup analyses showed that hypertension was associated with reduced AD signature cortical thickness only in APOE4 noncarriers, whereas hypertension was associated with elevated Aβ deposition in APOE4 carriers. Meanwhile, regardless of APOE4 status, AD dementia patients with hypertension had significantly lower Aβ deposition than those without hypertension. In conclusion, the findings suggest that hypertension contributes to AD primarily through the reduction of brain reserve. In case of APOE4 carriers, however, hypertension seems to additionally facilitate AD process through amyloid-dependent pathway.

1. Introduction

Increasing evidence suggests that hypertension contributes to the occurrence of Alzheimer's disease (AD) dementia (Gabin et al., 2017; Launer et al., 2000; Luchsinger et al., 2005), as well as vascular dementia (Gorelick et al., 2011; Iadecola, 2014), despite some conflicting reports (Guan et al., 2011; Rönnemaa et al., 2011). However, the pathophysiological mechanism underlying the relationship between hypertension and AD dementia still remains unclear.

Cerebral beta-amyloid (Aβ) accumulation and AD-pattern neurodegeneration are the 2 major pathophysiological processes of AD (Jack et al., 2013; Vemuri et al., 2017). Several previous studies investigated the relationship between hypertension and these 2 processes, but yielded conflicting results. The findings of a preclinical study indicated that hypertension increased cerebral Aβ accumulation through impairment of blood-brain barrier permeability (Gentile et al., 2009). A postmortem brain study (Petrovitch et al., 2000) and an amyloid imaging study (Langbaum et al., 2012) reported positive associations between blood pressure (BP) and the number of senile plaques in late-life or cerebral Aβ accumulation. By contrast, another postmortem brain study (Wang et al., 2009) and several neuroimaging studies of nondemented older adults (Glodzik et al., 2012; Gottesman et al., 2017; Vemuri et al., 2017) reported no association between hypertension and cerebral Aβ deposition.

In terms of AD-pattern neurodegeneration, magnetic resonance imaging (MRI) studies have demonstrated an association between

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hypertension and increased brain atrophy in regions associated with AD (Beauchet et al., 2013; Korf et al., 2004; Power et al., 2016; Vemuri et al., 2017; Wiseman et al., 2004). The findings suggested that hypertension may decrease brain reserve, which acts as passive protection capacity, via a greater brain volume or more synaptic connections, against the results of pathologic changes (Perneczky et al., 2010; Stern, 2012). Individuals with decreased brain reserve develop cognitive impairment or dementia with relatively lower pathological burden, such as Aβ accumulation. Not only directly, but hypertension may contribute indirectly to the neurodegeneration via increased Aβ accumulation.

To clarify complex relationship between hypertension, Aβ accumulation, and neurodegeneration, we used a clinical stage-specific approach, separately focusing on the cognitively normal (CN) stage and AD dementia stage. The Aβ accumulation begins at the asymptomatic stage of AD (i.e., CN) and saturates in the AD dementia stage (Pike et al., 2007; Rowe et al., 2007), whereas neurodegeneration gradually and continuously progresses through the stages of dementia despite beginning at the asymptomatic stage of AD (Jack et al., 2013). Given the differential progression of Aβ accumulation and neurodegeneration across the clinical stage of AD, the CN stage is appropriate for investigating the direct influence of hypertension on Aβ accumulation and neurodegeneration. The AD dementia stage provides an opportunity to identify the indirect consequence of direct influence (e.g., direct influence: aggravated neurodegeneration in CN; indirect consequence: less Aβ accumulation in AD dementia stage, as a consequence of lower brain reserve because of aggravated neurodegeneration). To date, few studies investigated the relationship between hypertension and AD biomarkers using the clinical stage-specific approach.

The apolipoprotein E ε4 (APOE4) allele has been established as a risk factor for AD (Corder et al., 1993). In several previous studies, APOE4 and vascular risk factors including hypertension have possible synergistic effects on Aβ accumulation (Rodrigue et al., 2013) or AD-related memory decline (Bangen et al., 2013; Tai et al., 2016; Zade et al., 2010). In addition, APOE4 is known to have a direct impact on vascular condition, disrupting the vascular endothelium and blood-brain barrier (Liu et al., 2013; Yu et al., 2014), and should be considered in investigating the effect of hypertension on Aβ accumulation and neurodegeneration.

That is why we aimed to elucidate the relationship of hypertension with Aβ and neurodegeneration biomarkers of AD in both CN and AD dementia individuals, simultaneously identifying the modulating effect of APOE4 on the relationship between hypertension and AD biomarkers.

2. Methods

2.1. Participants

Participants were recruited from the Korean Brain Aging Study for the Early Diagnosis and Prediction of Alzheimer's Disease (KBASE), an ongoing prospective cohort study that began in 2014. Details of the KBASE cohorts and recruitment and exclusion criteria have been described previously (Byun et al., 2017b). In brief, as of February 2017, the study includes a total 259 CN older adults and 79 individuals with AD dementia. The inclusion criteria for the CN group were (a) age between 55 and 90 years (inclusive); (b) no diagnosis of mild cognitive impairment or dementia; and (c) global Clinical Dementia Rating (CDR) (Morris, 1993) score of 0. Inclusion criteria for patients with AD dementia were as follows: (a) age between 55 and 90 years (inclusive); (b) meet both Diagnostic and Statistical Manual of Mental Disorders IV criteria for dementia and National Institute on Aging and Alzheimer's Association diagnostic criteria for probable AD dementia; and (c) global CDR score of 0.5 or 1. The study protocol was approved by the Institutional Review Boards of Seoul National University Hospital and SNU-SMG Boramae Center (Seoul, South Korea) and conducted in accordance with the recommendations of the current version of the Declaration of Helsinki. All subjects and/or caregivers provided written informed consent.

2.2. Clinical assessment

All participants were examined by trained psychiatrists with advanced training in dementia research according to the KBASE clinical assessment protocol which incorporates the Korean version of the Consortium to Establish a Registry for Alzheimer's Disease Assessment Packet (Lee et al., 2002). The severity of cognitive impairment was rated on the global CDR; the subscale scores were used to calculate the CDR sum of boxes (CDR-SOB).

Hypertension was defined as either a documented medical history of hypertension or treatment with antihypertensive medication. The classification was based on data collected by a thorough interview with participants and reliable information provided by trained nurses. Subjects who presented with high current BP (systolic/diastolic BP $\geq$ 140/90 mm Hg) (Chobanian et al., 2003) but had no diagnostic history of hypertension at the time of the study were not classified as hypertensive for main analyses. Comorbidity of vascular risk factors (VRFs) other than hypertension such as diabetes mellitus, hyperlipidemia, coronary artery disease, transient ischemic attack, and stroke were assessed in the same manner as evaluation of hypertension comorbidity. A VRF score (VRS) was calculated for the number of VRFs observed, other than hypertension, and reported as a percentage (DeCarli et al., 2004). In addition, smoking status (never/ex-smoker/current smoker) was also evaluated by interview. Systolic and diastolic BPs were measured 3 times at 5-minute intervals in the supine position after 5 minutes of rest by a trained nurse. The mean systolic and diastolic BP was used for the analysis.

2.3. Image data acquisition and processing

All subjects underwent simultaneous three-dimensional (3D) [^{11}C] Pittsburg compound B (PiB)—positron emission tomography (PET) and 3D T1-weighted MRI using a 3.0 T Biograph mMR (PET-MR) scanner (Siemens, Washington DC, USA) according to the manufacturer's approved guidelines. Details of [^{11}C] PiB-PET imaging and MR imaging acquisition and preprocessing have been described previously (Byun et al., 2017a). The automatic anatomic labeling algorithm and a region combining method (Reiman et al., 2009) were applied to determine regions of interests (ROIs) to establish the ^{11}C-PiB retention level in the frontal, posterior cingulate-precuneus, lateral temporal, and lateral parietal regions. The standardized uptake value ratio (SUVR) for each ROI was calculated by dividing the mean value for all voxels within each ROI by the mean cerebellar uptake value in the same image. Global Aβ deposition SUVR was calculated by dividing the voxel-weighted mean uptake value of 4 ROIs by the mean cerebellar uptake value (Choe et al., 2014; Reiman et al., 2009). Subjects were classified as Aβ-positive if the SUVR was $>$1.4 in at least 1 of the 4 ROIs, and as Aβ-negative if the SUVR of all 4 ROIs was $\leq$1.4 (Jack et al., 2014; Reiman et al., 2009). For voxelwise analysis of PiB-PET images, Statistical Parametric Mapping 12 (SPM12; Institute of Neurology, University College of London, UK) implemented on MATLAB 2014a (Mathworks, Inc; Natick, MA, USA) was used. The [^{11}C] PiB-PET data from each subject were coregistered to individual T1-weighted MR images and then automatically spatially normalized into the standard MNI template in SPM12 using transformation parameters derived from the normalization of individual MR images to the template. All normalized images were reformatted with a $1 \times 1 \times 1$ mm voxel. The

cerebellum was used as a reference for quantitative normalization of cerebral [^{11}C] PiB uptake values (Lopresti et al., 2005).

For AD-specific neurodegeneration, the AD signature cortical thickness (AD-CT) was calculated for each participant. AD-CT was defined as the mean cortical thickness value obtained from AD signature regions, including the middle temporal, entorhinal, inferior temporal, and fusiform gyrus, according to a previous study (Jack et al., 2014). Voxel-based morphometry (VBM) analysis was performed using SPM12 to demonstrate group differences in regional gray matter (GM) density between the hypertension and no-hypertension groups in each diagnostic state. All T1-weighted images of each subject were normalized into standard anatomical space using MNI 152 template with a linear 12-parameter affine transformation. Normalized images were segmented into GM, white matter, and cerebrospinal fluid. Smoothing at 12-mm full width at half maximum was performed after segmentation and modulation.

To obtain the volume of white matter hyperintensities (WMHs), we used a validated automatic procedure published previously (Tsai et al., 2014) with 2 modifications in the current processing procedure. An optimal threshold of 70 was applied compared with the threshold of 65 used in the original article as it was more suitable for the data. In addition, we did not use diffusion-weighted imaging in the current automated procedure because individuals with acute cerebral infarcts were not enrolled in our study. Final WMH candidate images were used to extract WMH volumes based on lobar ROIs in native space of each subject (Kochunov et al., 2001).

2.4. Blood test and APOE genotyping

Blood sampling was completed and DNA was extracted from whole blood. APOE genotyping was carried out as previously described (Wenham et al., 1991). APOE4 carrier status was coded if at least 1 ε4 allele was present.

2.5. Statistical analysis

The clinical and demographic characteristics were compared for continuous data using independent *t*-test and categorical data using a χ^2 test. Comparison of cerebral Aβ deposition and AD-CT between the hypertension and no-hypertension groups in CN and AD dementia subjects were tested with analyses of covariance (ANCOVAs) for continuous variables, or logistic regressions for categorical variables using the enter method with an adjustment for age, sex, and APOE4 carrier status (model 1). Additional models were prepared adjusting for VRS (model 2) or volume of WMHs (model 3). A CDR-SOB was added as a covariate for the model for AD dementia (model 4). To test the moderating effect of APOE4, a hypertension ×APOE4 interaction term was added to the model including age, sex, hypertension, and APOE4 status. If the interaction term was significant, subsequent post hoc analyses were performed with Bonferroni correction for each APOE4 carrier and noncarrier subgroup. As a sensitivity analysis, we repeated above-mentioned statistical analyses after adding subjects with high current BP (systolic/diastolic BP ≥ 140/90 mm Hg) (Chobanian et al., 2003) at the time of examination to the hypertensive group. We also repeated the ANCOVAs and logistic regression analyses, this time controlling for current systolic/diastolic BP or smoking status, as well as VRS and demographic variables, for additive control of their effects. All statistical analyses were conducted using the SPSS software (version 22.0, SPSS Inc; Chicago, IL, USA), and two-tailed *p* values <0.05 were considered statistically significant.

Differences in regional cerebral Aβ deposition and GM atrophy on a voxel-based analysis between the hypertension and no-hypertension groups within CN and AD dementia groups (CN_{noHTN} vs. CN_{HTN} and AD_{noHTN} vs. AD_{HTN}) were estimated using ANCOVA with age, sex, and APOE4 as covariates on SPM 12. For the voxel-based analyses, results were displayed at $p < 0.005$ (uncorrected) with an extent threshold >1062 contiguous voxels. This cluster size threshold was applied for multiple comparison corrections, according to a cluster correction procedure using 3dClusSim in Analysis of Functional and Neural image software, with 10,000 iterations of Monte Carlo simulations on anatomical cerebral mask data set (Forman et al., 1995).

3. Results

3.1. Comparison of cerebral Aβ deposition between subjects with versus without hypertension in CN and AD dementia groups

The demographic and clinical characteristics of subjects are summarized in Table 1. There were no significant differences in

Table 1
Demographics and clinical characteristics of participants

Characteristics	CN (n = 259)			AD dementia (n = 79)		
	CN_{noHTN} (n = 141)	CN_{HTN} (n = 118)	*p*-value	AD_{noHTN} (n = 46)	AD_{HTN} (n = 33)	*p*-value
Age (y)	67.2 ± 7.9	70.5 ± 7.8	0.001	71.5 ± 7.9	74.2 ± 8.1	0.151
Sex (Female)	67 (47.5%)	66 (55.9%)	0.16	33 (71.7%)	22 (66.7%)	0.629
Education (y)	12.3 ± 4.4	11.3 ± 5.0	0.079	8.7 ± 5.1	9.8 ± 5.8	0.410
APOE4 carrier	23 (16.3%)	24 (20.3%)	0.402	27 (58.7%)	20 (60.6%)	0.865
CDR-SOB				5.23 ± 1.36	4.80 ± 1.62	0.209
SBP (mm Hg)	122.4 ± 17.5	127.3 ± 15.2	0.018	122.3 ± 16.4	126.3 ± 15.3	0.283
DBP (mm Hg)	76.3 ± 11.6	77.4 ± 10.2	0.413	75.2 ± 13.5	78.5 ± 9.4	0.249
Onset age of hypertension (y)		61.8 ± 9.1			62.8 ± 10.4	
Duration of hypertension (y)		8.8 ± 7.1			11.4 ± 9.4	
Antihypertensive medication		115 (97.5%)			32 (97.0%)	
Diabetes Mellitus	18 (12.7%)	28 (23.7%)	0.02	6 (13.0%)	6 (18.2%)	0.543
Coronary artery disease	3 (2.1%)	10 (8.5%)	0.019	2 (4.3%)	3 (9.1%)	0.644
Hyperlipidemia	36 (25.4%)	51 (43.2%)	0.01	9 (19.6%)	17 (51.5%)	0.004
Stroke	0	0		0	0	
TIA	1 (0.01%)	1 (0.01%)		0	0	
VRS (%)	8.1 ± 12.2	15.3 ± 14.5	<0.001	7.4 ± 12.2	15.8 ± 15.6	0.009
WMH volume	5.317 ± 5.180	6.130 ± 5.818	0.259	4.928 ± 4.646	7.056 ± 4.231	0.070

Data for presented as means ± SD for continuous variables and as N (%) for categorical variables.
Key: CN, cognitively normal; CN_{noHTN}, CN without hypertension; CN_{HTN}, CN with hypertension; AD, Alzheimer's disease; AD_{noHTN}, AD without hypertension; AD_{HTN}, AD with hypertension; APOE4, apolipoprotein E ε4; CDR-SOB, Clinical Dementia Rating sum of box; SBP, systolic blood pressure; DBP, diastolic blood pressure; VRS, vascular risk factor score; TIA, transient ischemic attack; WMH, white matter hyperintensity.

global Aβ deposition or Aβ positivity rates between the CN with hypertension (CN_{HTN}) and CN without hypertension (CN_{noHTN}) groups (Table 2, Fig. 1A). By contrast, the AD dementia with hypertension (AD_{HTN}) group had significantly lower global Aβ deposition and Aβ positivity rates compared with the AD dementia without hypertension (AD_{noHTN}) group. Adjustment for VRS, WMH volume, or CDR-SOB did not affect the results (Table 2).

Voxel-based analyses of [^{11}C] PiB-PET did not detect any difference in regional Aβ deposition between the CN_{HTN} and CN_{noHTN} groups. Conversely, the AD_{HTN} group had less Aβ deposition compared with the AD_{noHTN} group in the bilateral cerebral cortices including the precuneus and cingulate regions, as well as putamen and globus pallidus (Fig. 2A). No brain region in the AD_{HTN} group displayed a higher Aβ deposition than the AD_{noHTN} group (Fig. 2B). To demonstrate the spatial distribution of Aβ deposition in AD_{noHTN} and AD_{HTN}, we performed additional voxel-based comparisons of the regional Aβ deposition between each AD group and the CN group. Although the AD_{noHTN} had greater Aβ deposition in widespread brain regions compared with the CN group, AD_{HTN} had greater Aβ deposition in more restricted regions, including the orbitofrontal and inferior temporal cortices, precuneus, and basal ganglia (Supplemental Material Fig. S1).

3.2. Comparison of neurodegeneration between subjects with versus without hypertension in CN and AD dementia groups

The CN_{HTN} group exhibited significantly lower AD-CT than the CN_{noHTN} group (Table 2, Fig. 1B), even controlling for VRS or WMH volume (Table 2). No difference in AD-CT was observed between the AD_{HTN} and AD_{noHTN} groups, even after additively controlling for CDR-SOB, VRS, or WMH (Table 2). The pattern of results remained the same when global Aβ deposition was added as an additional covariate to model 1 ($p < 0.001$ and $p = 0.421$ for CN and AD dementia, respectively).

VBM analysis also showed that the CN_{HTN} group had significantly lower GM density in the frontal, insula, posterior cingulate, medial temporal, medial occipital and lateral temporo-occipital cortex, and thalamus than the CN_{noHTN} group (Fig. 3A). The CN_{HTN} group did not have higher GM density in any cerebral region than the CN_{noHTN} group (Fig. 3B). No significant difference in regional GM density was observed between the AD_{HTN} and AD_{noHTN} groups.

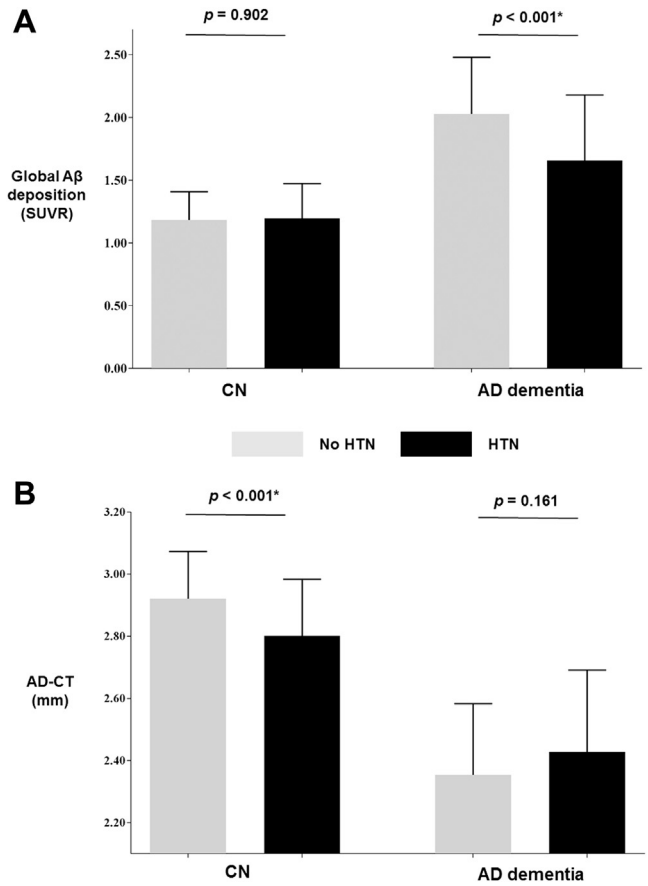

Fig. 1. Comparison of AD biomarkers in each diagnostic group. Comparison of (A) cerebral Aβ deposition and (B) AD-CT between subjects without hypertension (no HTN) and those with hypertension (HTN) in each diagnostic group. Gray bars represent subjects in no HTN group and black bars represent subjects with HTN group. The *p*-value is based on analysis of covariance adjusted for age, sex, and APOE4. Abbreviations: AD, Alzheimer's disease; AD-CT, Alzheimer's disease signature-cortical thickness; APOE4, apolipoprotein E ε4; HTN, Hypertension; SUVR, standardized uptake value ratio.

3.3. Modulating effect of APOE4 on the relationship of hypertension with cerebral Aβ deposition and neurodegeneration

A significant hypertension × APOE4 interaction was observed on both global Aβ deposition and AD-CT in CN group (Table 3). Subsequent subgroup analyses indicated that the CN_{HTN} group had

Table 2
Comparison of cerebral Aβ deposition and neurodegeneration between subjects with versus without hypertension in CN and AD dementia groups

Variables	CN (n = 259)					AD dementia (n = 79)					
	CN_{noHTN} (n = 141)	CN_{HTN} (n = 118)	p^a	p^b	p^c	AD_{noHTN} (n = 46)	AD_{HTN} (n = 33)	p^a	p^b	p^c	p^d
Cerebral Aβ deposition											
Global Aβ deposition	1.17 ± 0.20	1.20 ± 0.28	0.902	0.855	0.944	2.04 ± 0.45	1.65 ± 0.53	<0.001	0.003	0.007	<0.001
Aβ positivity	17 (12.0%)	11 (9.3%)	0.268	0.381	0.234	41 (89.1%)	21 (63.6%)	0.007	0.037	0.042	0.007
Neurodegeneration											
AD-CT	2.93 ± 0.15	2.79 ± 0.18	<0.001	<0.001	<0.001	2.38 ± 0.23	2.43 ± 0.30	0.161	0.193	0.179	0.337

Data are presented as mean ± SD for continuous variables and as N (%) for categorical variables.
Key: CN, cognitively normal; CN_{noHTN}, CN without hypertension; CN_{HTN}, CN with hypertension; AD, Alzheimer's disease; AD_{noHTN}, AD without hypertension; AD_{HTN}, AD with hypertension; Aβ, beta-amyloid; AD-CT, AD signature cortical thickness; APOE4, apolipoprotein E ε4; VRS, vascular risk factor score; CDR SOB, Clinical Dementia Rating sum of box.
[a] Model 1: adjusted for age, sex and APOE4.
[b] Model 2: adjusted for age, sex, APOE4 and VRS.
[c] Model 3; model 1 + volume of white matter hyperintensity.
[d] Model 4; model 1 + CDR-SOB (only for AD dementia).

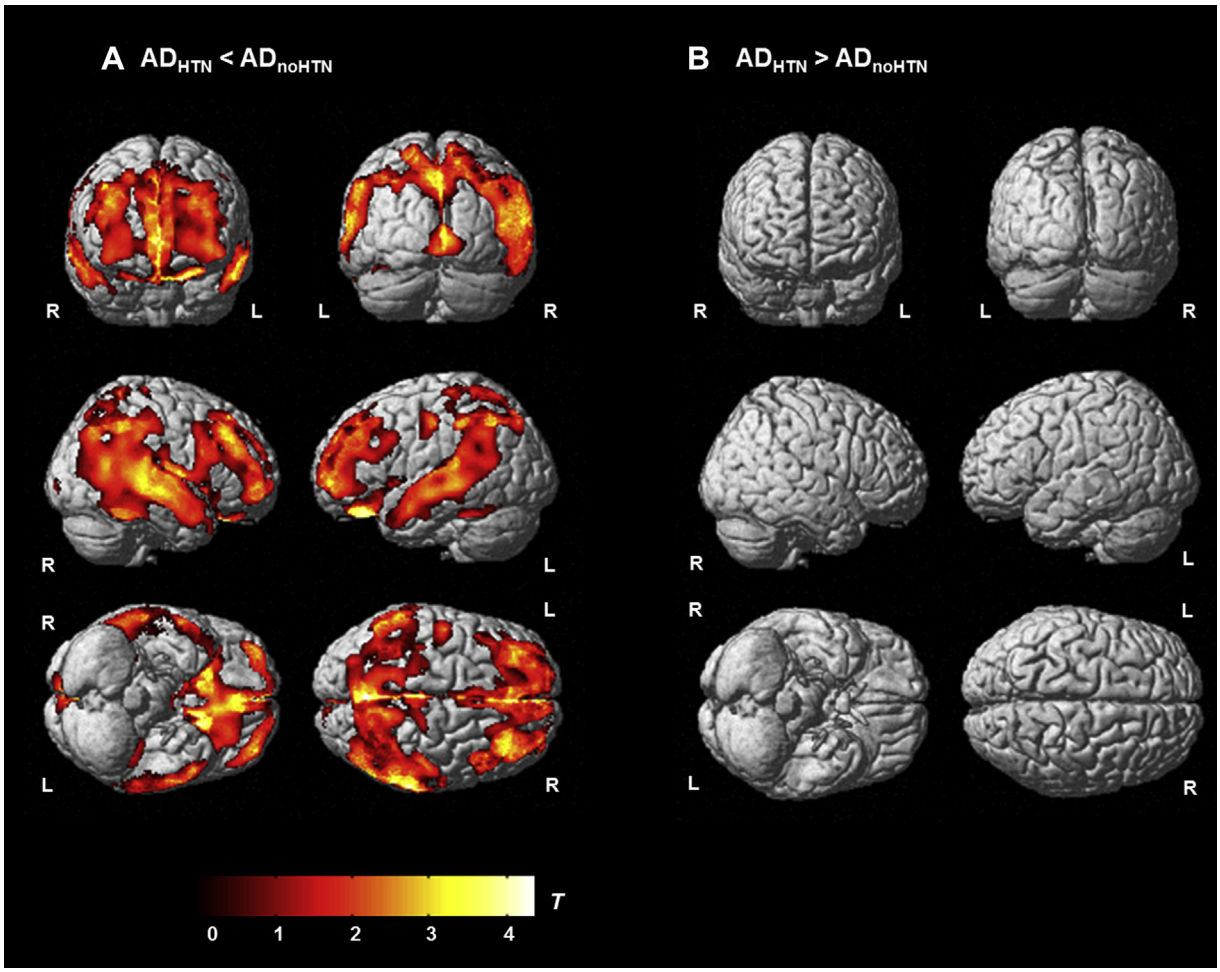

Fig. 2. SPM results showing difference of cerebral Aβ deposition in AD_{HTN} and AD_{noHTN}. Statistical parametric maps showing difference of cerebral Aβ deposition between subjects in the AD_{HTN} and AD_{noHTN} groups after controlling the effects of age, sex, and APOE4 ($p < 0.005$ [uncorrected], $k > 1062$; cluster-correction procedure for multiple comparison correction was applied). (A) $AD_{HTN} < AD_{noHTN}$ and (B) $AD_{HTN} > AD_{noHTN}$. Abbreviations: SPM, statistical parametric maps; Aβ, beta-amyloid; AD, Alzheimer's disease; AD_{HTN}, AD with hypertension; AD_{noHTN}, AD without hypertension; APOE4, apolipoprotein E ε4.

significantly higher global Aβ than the CN_{noHTN} group in APOE4 carriers (Fig. 4A). No differences in Aβ burden in noncarriers was observed between CN_{HTN} and CN_{noHTN} groups. Similar hypertension × APOE4 interaction effect was also observed on AD-CT in the CN group (Table 3). Subgroup analysis demonstrated that the CN_{HTN} group had significantly lower AD-CT than the CN_{noHTN} group in APOE4 noncarriers (Fig. 4B). There was no significant difference in AD-CT between the CN_{HTN} and CN_{noHTN} groups in APOE4 carriers.

The effect of the hypertension × APOE4 interaction on global Aβ deposition and AD-CT was not significant with respect to AD dementia (Supplemental Material: Table S1).

3.4. Sensitivity analyses

We first repeated aforementioned analyses by including subjects with high current BP (i.e., systolic/diastolic BP ≥ 140/90 mm Hg) as in the hypertensive group for sensitivity analyses. The overall results of group comparisons (Supplemental Material: Table S2), modulating effect of APOE4 (Supplemental Material: Table S3) and subgroup analysis (Supplemental Material: Table S4) were not changed. Additional controlling of current systolic and diastolic BP as covariates also did not change the results (Supplemental Material: Table S5). Finally, when smoking status was added to the logistic regression analysis as a covariate with the other variables including VRS and demographic variables (i.e., age, sex, and APOE4 status), the result did not change (Supplemental Material: Table S6).

4. Discussion

This study investigated the relationship between hypertension and AD biomarkers using a clinical stage-specific approach, separately focusing on CN and AD dementia stage. In the CN group, hypertension was associated with reduced AD-CT, but was not related to cerebral Aβ deposition. In AD dementia group, however, hypertension was associated with lower Aβ deposition but not with AD-CT, even after controlling for clinical severity of dementia.

It is well known that cerebral Aβ deposition in the brain begins decades before cognitive symptoms appear (Jack et al., 2013). Therefore, if hypertension contributes to AD dementia because of amyloid pathology, CN_{HTN} subjects would have higher cerebral Aβ burden compared with CN_{noHTN} ones. Aβ burden, however, was not different between the 2 groups, whereas AD-CT was lower in the CN_{HTN} group. These results indicate that hypertension probably contributes to AD development primarily through amyloid-independent processes, such as aggravation of neurodegeneration. Given the similar level of Aβ burden, therefore,

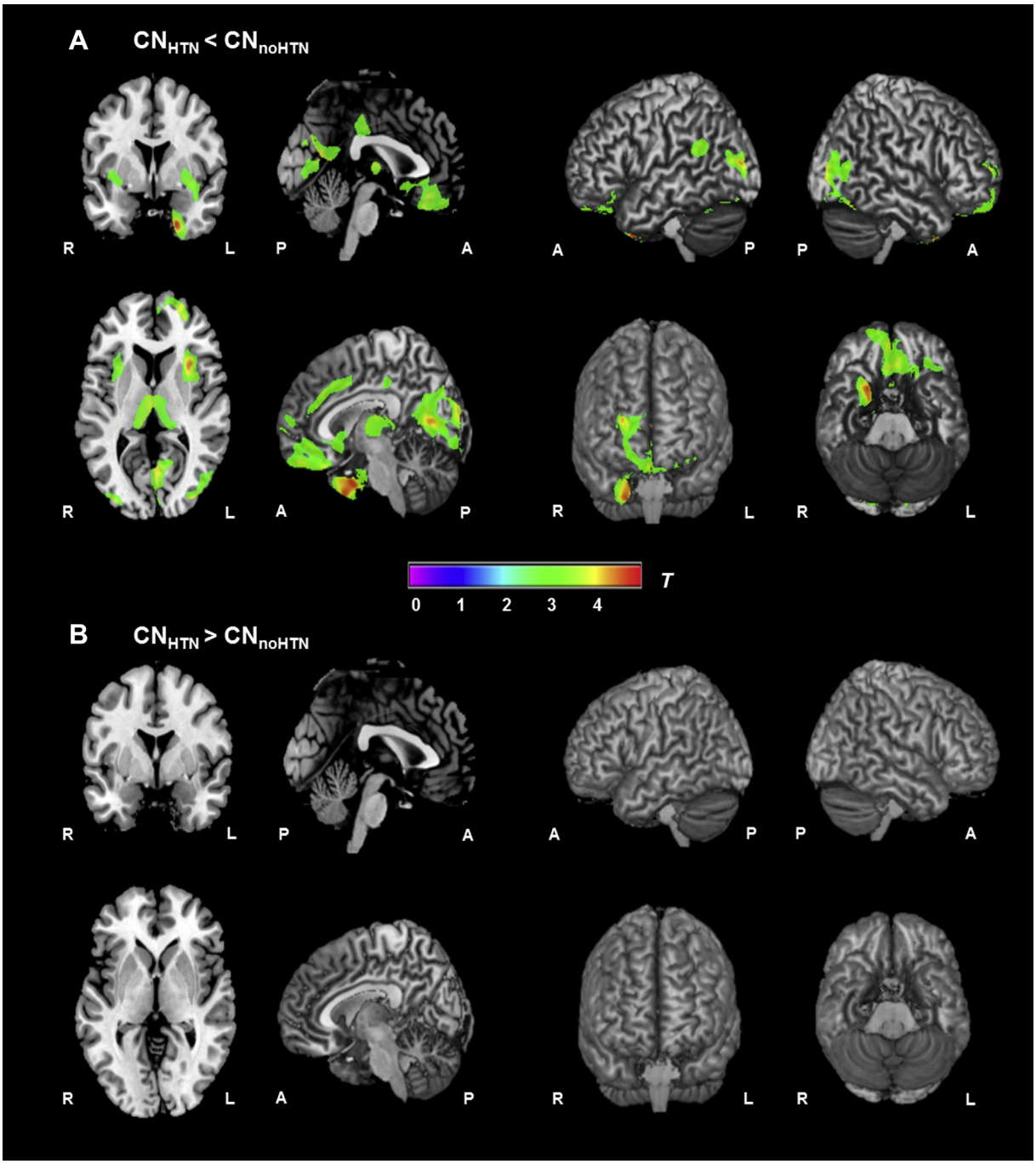

Fig. 3. SPM results showing difference of regional gray matter volume in CN_{HTN} and CN_{noHTN}. Statistical parametric maps showing difference of regional gray matter volume between subjects in the CN_{HTN} and CN_{noHTN} after controlling the effects of age, sex, and APOE4 ($p < 0.005$ [uncorrected], $k > 1062$; cluster-correction procedure for multiple comparison correction was applied): (A) $CN_{HTN} < CN_{noHTN}$, and (B) $CN_{HTN} > CN_{noHTN}$. Abbreviations: SPM, statistical parametric maps; AD, Alzheimer's disease; APOE4, apolipoprotein E ε4; CN_{HTN}, CN with hypertension; CN_{noHTN}, CN without hypertension.

individuals with hypertension are more likely to develop dementia than those without hypertension because of relatively lower brain reserve (Stern, 2012) caused by aggravated neurodegeneration. The finding of lower Aβ burden in AD_{HTN} compared with AD_{noHTN} with similar dementia severity also supports this possibility. A previous study with a different population indicated that patients with AD dementia with a lower cerebral Aβ burden had a higher frequency of hypertension history compared with those with higher Aβ burden (Jeon et al., 2016). In addition, our study is in line with previous studies in which individuals with pre-existing deficits or vulnerabilities could manifest a clinical AD dementia syndrome despite underlying non-AD or mixed pathologies, such as vascular and other neurodegenerative diseases (Jeon et al., 2016; Landau et al., 2016; Schneider et al., 2007). Further study will be necessary to elucidate the exact mechanism of hypertension-related neurodegeneration.

With respect to the relationship between hypertension and cerebral Aβ burden, the negative results of this study for the CN group correspond to several previous reports. A cross-sectional study reported no association of cerebrospinal fluid Aβ with hypertension

Table 3
Interaction effects of hypertension and APOE4 status on global Aβ deposition and AD-CT in CN group

Variables	Coefficient	SE	*t*	*p*[a]
Global Aβ deposition				
Hypertension x APOE4	0.165	0.076	2.173	0.031
AD-CT				
Hypertension x APOE4	0.123	0.045	2.716	0.007

Key: APOE4, apolipoprotein E ε4; Aβ, beta-amyloid; AD-CT, Alzheimer's disease signature cortical thickness; CN, cognitively normal; SE, standard error.
[a] Adjusted for age, sex, hypertension and APOE4 carrier status.

in CN old adults (Glodzik et al., 2012). The Adult Changes in Thought study also reported that midlife BP was not associated with density of neuritic plaques in postmortem brains (Wang et al., 2009). A longitudinal study, using PiB-PET, also demonstrated that midlife hypertension was not associated with Aβ deposition in CN subjects (Vemuri et al., 2017). However, several other studies have indicated that hypertension may increase AD risk via direct effects on Aβ pathology. A postmortem study reported that midlife high BP is associated with increased neuritic plaques (Petrovitch et al., 2000). A PiB-PET study with a small sample size demonstrated that BP is positively correlated with cerebral amyloid burden in CN (Langbaum et al., 2012). The discrepancies may be partially explained by the modulation effect of APOE4 on the relationship between hypertension and Aβ burden demonstrated in this study. In this study, the CN_{HTN} subjects had a greater Aβ burden than CN_{noHTN} subjects among the APOE4 carriers, whereas the Aβ burden did not differ between the CN_{HTN} and CN_{noHTN} subjects among the APOE4 noncarriers. Considering the frequency of APOE4 carriers in the CN group (18.1%), which was similar to the frequency of APOE4 carriers in an Asian population (16.3%) reported in a meta-analysis (Farrer et al., 1997; Kim et al., 1999), the results for the CN group in our study were more likely to be influenced by APOE4 noncarriers (81.9%) than by carriers. In this context, a previous PiB-PET study that reported positive associations between an elevated BP and Aβ burden may be explained by the higher proportion of APOE4 carriers (59.3%) (Langbaum et al., 2012).

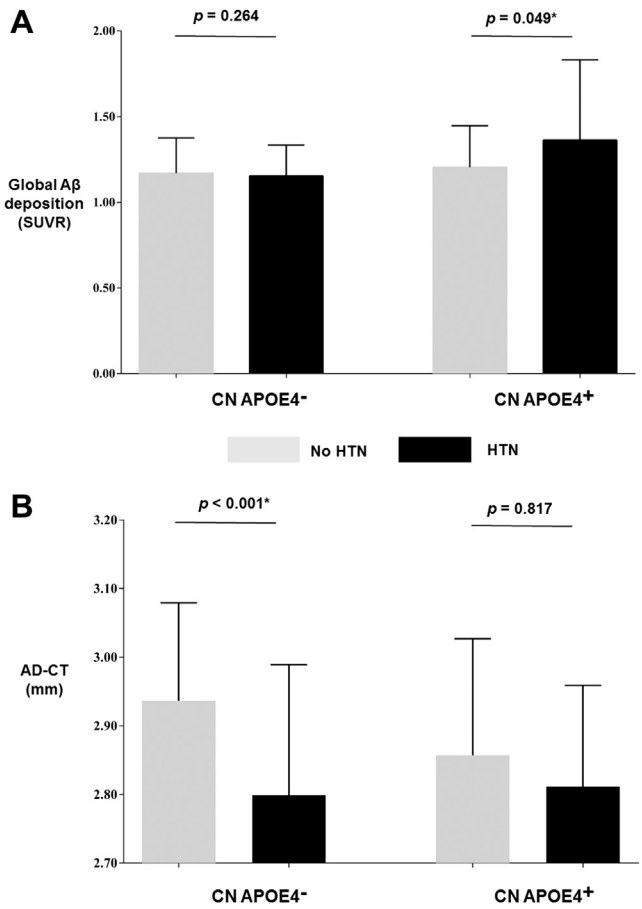

Fig. 4. Aβ deposition and AD-CT stratified by hypertension and APOE4. Bar graphs represent mean and standard error of (A) cerebral Aβ deposition and (B) AD-CT in subjects without hypertension (No HTN; gray bar) and with hypertension (HTN; black bar) stratified by APOE4 carrier status in CN subjects. *Bonferroni corrected $p < 0.05$ after controlling the effect of age and sex. Abbreviations: Aβ, beta-amyloid; CN APOE4 −, CN without APOE4 carrier; CN APOE4 +, CN with APOE4 carrier; AD, Alzheimer's disease; AD-CT, AD-signature cortical thickness; APOE4, apolipoprotein E ε4.

A recent study demonstrated that APOE4 promotes inflammatory cascades that result in neurovascular dysfunction including blood-brain barrier breakage and leakage of toxic proteins into the brain tissue (Bell et al., 2012). This type of APOE4-dependent damage to neurovascular systems can contribute to Aβ accumulation (Liu et al., 2013). In this context, hypertension-induced cerebrovascular injury may synergistically interact with APOE4-dependent neurovascular damage, exacerbating cerebral amyloid deposition.

Although the AD_{HTN} group had less Aβ deposition compared with the AD_{noHTN} group, the AD_{HTN} group had greater Aβ deposition in certain brain regions, particularly the orbitofrontal and inferior temporal cortices, and precuneus (Figure S1 in the supplemental Material), compared with CN group. These are the brain regions where amyloid plaques accumulate in the earliest phase of AD process (i.e., Braak stage A and Thal stage 1) (Braak and Braak, 1991; Thal et al., 2002), when clinical status is still cognitively asymptomatic (Villeneuve et al., 2015). This finding implies that clinical dementia or prominent cognitive impairment manifests with the earliest regional involvement of amyloid accumulation during the AD process in individuals with hypertension, again supporting the possibility of a hypertension-related lower brain reserve.

CN_{HTN} individuals exhibited decreased AD-CT compared with CN_{noHTN} individuals. VBM analysis indicated significant GM atrophy in multiple brain regions in the CN_{HTN} group compared with the CN_{noHTN} group. These results correspond to the findings of several previous MRI studies with CN that found a significant association between hypertension and overall or regional reduction in brain volume (Beauchet et al., 2013; Glodzik et al., 2012; Jack et al., 2014; Wiseman et al., 2004). In terms of the possible underlying mechanisms, increased thickness of tunica media in cerebral vasculature followed by a narrowing in the lumen size, which may contribute to brain atrophy secondary to impaired cerebral autoregulation, hypoperfusion, and ischemia (Gąsecki et al., 2013). Previous studies suggested that hypertension indirectly contributes to GM atrophy through white matter damage (Liao et al., 1997). However, we found that controlling for WMH volume (model 3) did not affect the significant association observed between hypertension and reduced AD-CT, indicating that the influence of hypertension is directly related to GM injury, independent of an indirect pathway via white matter injury. Hypertension-associated reduction of AD-CT in CN was significant only in APOE4 noncarriers. The exact mechanism underlying the differential association depending on APOE4 carrier status is not clear. The relatively small sample size of the APOE4 carrier CN group (n = 47) makes difficult to detect a difference based on the presence of hypertension, compared with the noncarrier CN group (n = 212). In addition, considering that APOE4 itself can independently aggravate neurodegeneration (Shi et al., 2017), and APOE4 carriers showed more severe brain atrophy than noncarriers (Reiter et al., 2017), direct effect of APOE4 on the neurodegeneration might override the effect of hypertension-

related neurodegeneration in APOE4 carriers compared with non-carriers in CN individuals in this study.

The hypertension group was defined as the individuals with either a documented history of high BP or treatment with antihypertensive medication in this study. Many longitudinal studies and meta-analyses suggest that midlife high BP is more important than late-life high BP with respect to AD dementia risk (Beauchet et al., 2013; McGrath et al., 2017; Qiu et al., 2005). Moreover, BP begins to decrease over 3 years before dementia diagnosis and afterward (Qiu et al., 2004; Skoog et al., 1996). Therefore, we considered only the history of hypertension diagnosis or treatment instead of current BP. Sensitivity analysis which included subjects with high current BP (systolic/diastolic BP $\geq$ 140/90 mm Hg) (Chobanian et al., 2003) in the hypertensive group, and the other, which controlled current SBP and DBP as covariates, did not affect the results of group comparisons and interaction analyses.

This study has several strengths. First, we examined the effect of hypertension on AD biomarkers through a clinical stage-specific approach, focusing on CN and AD dementia stages using multimodal imaging. This approach made it possible to clarify the complex relationship between hypertension, Aβ accumulation, and neurodegeneration according to the clinical stages, even when accounting for the modulating effect of APOE4. Second, a relatively large sample size, particularly of the CN group, allowed clarification of the complex associations. Third, controlling for potential confounding factors, such as other vascular factors, WMH volume, age and sex, permitted a clear explanation of the mechanism linking hypertension, and AD dementia risk.

Nevertheless, some limitations need to be mentioned. First, as this study had a cross-sectional design, temporal or causal association between hypertension and AD biomarkers requires further verification in longitudinal studies. Second, the sample characteristics of our participants limit the generalizability of the findings. As individuals with a history of stroke or severe vascular lesions including infarcts and hemorrhages on brain MRI were excluded from the present study (Byun et al., 2017b), it is difficult to generalize the results to those with severe cerebrovascular lesions. In addition, most of the individuals in the hypertension group (97.5% and 97.0% of CN_{HTN} and AD_{HTN}, respectively) had taken antihypertensive medications, and the mean SBP/DBP of the hypertensive participants was relatively well-controlled (i.e., <130/80 mm Hg). Considering previous studies that reported an association between the use of antihypertensive drugs and the risk of AD dementia (Haag et al., 2009; Peila et al., 2006; Tully et al., 2016), the influence of hypertension on AD biomarkers may have been weakened by the sample characteristics in our study. Future studies involving participants with a higher vascular burden, such as those with poorly controlled BP or with severe WMH, are needed to extend the generalizability of our results.

5. Conclusions

In conclusion, the current findings suggest that hypertension contributes to AD primarily through the reduction of brain reserve because of direct GM injury. In case of APOE4 carriers, however, hypertension seems to additionally facilitate AD process through amyloid-dependent pathway. Besides that, different cerebral Aβ levels in AD dementia according to the presence of hypertension indicate that hypertension history should be considered when designing or interpreting clinical trials of antiamyloid therapy.

Disclosure statement

The authors have no competing interests to declare.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.neurobiolaging.2018.11.001.

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