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White matter microstructure disruptions mediate the adverse relationships between hypertension and multiple cognitive functions in cognitively intact older adults

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ABSTRACT

Although hypertension is a prominent vascular risk factor for late-life cognitive decline, the underlying pathophysiological mechanism remains unclear. Accordingly, the aim of this study was to examine the role of white matter microstructural integrity in hypertension-related cognitive detriments. We recruited 66 cognitively normal older adults, comprising 41 hypertensive patients and 25 normotensive controls. All participants underwent a comprehensive neuropsychological battery. White matter microstructural integrity was assessed using a tract-based automatic analysis approach derived from diffusion spectrum imaging. Mediating effects of white matter integrity were evaluated using structural equation modeling analyses. The results revealed that hypertensive older adults displayed poorer processing speed, executive function, and memory encoding. Lower white matter microstructural integrity was observed in the hypertensive elderly patients, primarily in long-range association fiber bundles. In particular, low microstructural integrity in specific tract bundles connecting frontal and posterior cerebral regions was found to underlie the adverse relationships between hypertension and multiple cognitive domains, including processing speed, executive function, memory encoding, and memory retention. Our findings suggest that hypertension may impair multiple cognitive functions by undermining white matter microstructures, even in cognitively intact older adults, thus further highlighting the necessity of monitoring vascular health to prevent cognitive decline.

1. Introduction

Vascular contributions to cognitive impairment have been established as the second most common cause of cognitive decline in later life, after Alzheimer's disease (Levine and Langa, 2011; Lobo et al., 2000). Among various vascular risk factors, hypertension has been considered the major contributor to cognitive decline (Gorelick et al., 2011; Iadecola et al., 2016). Abundant evidence from cross-sectional and longitudinal studies indicates that individuals with midlife hypertension display poorer performance in multiple cognitive domains in both midlife and later life compared with normotensive individuals. Specifically, processing speed and executive function (Brady et al., 2005; Bucur and Madden, 2010; de Moraes et al., 2002; Iadecola et al., 2016; Jacobs et al., 2013; Raz et al., 2003; Saxby et al., 2003) and, to a lesser extent, learning and memory ability (Brady et al., 2005; Hannesdottir et al., 2009; Saxby et al., 2003) have been demonstrated to be the cognitive domains most susceptible to the adverse effect of hypertension.

Most studies have examined pairwise associations between either hypertension and cognitive decline or hypertension and brain variables. However, the pathophysiological mechanism underlying the relationship between hypertension and cognitive decline remains uncharacterized. Multiple lines of evidence indicate a potential role of cerebral white matter in mediating the associations between hypertension and cognitive impairment. First, the brain's vasculature arrangement renders cerebral

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white matter especially vulnerable to the adverse effect of hypertension (Iadecola, 2013). Compared with gray matter, white matter structures are located at relatively distal regions of the vascular territories and are therefore more susceptible to the effects of hypoperfusion and hypoxia (Pantoni and Garcia, 1997), which are among the detrimental effects of hypertension (Tzourio et al., 2014). Second, studies investigating vascular contributions to brain pathology have consistently revealed that hypertension increases the risk of pathologic changes in cerebral white matter, including incipiently reduced microstructural integrity in normal-appearing white matter fibers and subsequent white matter macrostructural lesions (de Groot et al., 2013; Power et al., 2017; Sierra and Coca, 2006). Hypertension-related pathologic changes more commonly appear in periventricular white matter areas containing a high density of long-range fiber bundles than in deep subcortical white matter areas with relatively short fiber bundles (Henskens et al., 2009; Raz et al., 2007; Yoshita et al., 2006). In particular, hypertension has been demonstrated to be associated with lower microstructural integrity primarily in long-range fiber bundles extending from more anterior cerebral regions—such as the forceps minor (F*min*, the anterior portion of the corpus callosum), bilateral inferior frontal-occipital fasciculi (IFOF), superior longitudinal fasciculi (SLF), inferior longitudinal fasciculi (ILF), uncinate fasciculi (UF), the body section of the cingulum bundle (CG*body*), and anterior thalamic radiations (ATR) (de Groot et al., 2015; Maillard et al., 2012; McEvoy et al., 2015; Salat et al., 2012; Suzuki et al., 2017)—and, less commonly, in fiber bundles extending from more posterior cerebral regions such as the splenium (i.e., part of the forceps major (F*maj*), which is the posterior portion of the corpus callosum) (Gons et al., 2012). Finally, pathologic disruptions in cerebral white matter have been reported to be predominantly associated with processing speed and executive function (Cremers et al., 2016; Kennedy and Raz, 2009; Salami et al., 2012; Tuladhar et al., 2015) and, less frequently, learning and memory (Kennedy and Raz, 2009; Voineskos et al., 2012). The correspondence between cognitive domains affected by both hypertension and white matter pathology further indicates a potential mediating effect of pathologic disruptions in white matter integrity on hypertension-related cognitive detriments.

However, little research has been undertaken to elucidate the mediating effect of disrupted white matter microstructural integrity on the relationship between hypertension and cognitive detriments. Although some studies have indirectly addressed this question by examining pairwise correlations among hypertension, white matter microstructural integrity, and cognitive detriments (e.g., Hannesdottir et al., 2009; Leritz et al., 2010), to our knowledge, only two studies (Jacobs et al., 2013; Li et al., 2016) have directly evaluated the mediating effect of white matter microstructural integrity on the relationship between hypertension and cognitive detriments. However, the methodological limitations of these two studies make it difficult to validate any possible mediating effect of white matter structural integrity on the mentioned relationship. Specifically, both of these studies have employed only a few cognitive measures and limited their investigation to only one of the subcomponents (e.g., either switching or inhibition) of the executive function domain; they failed to include tests for other major executive function subcomponents (e.g., abstract reasoning and working memory) or measures examining other cognitive domains that are reportedly related to hypertension status (Jacobs et al., 2013; Li et al., 2016). In addition, these two studies have included participants with mixed cognitive status (e.g., cognitively normal individuals, mild cognitive impairment patients, or possible dementia cases), rendering their results difficult to explain and generalize due to confounding by possibly neurodegenerative pathophysiological mechanisms underlying the tested sample. Furthermore, most studies have measured white matter microstructural integrity primarily through a voxel-based analysis derived from diffusion tensor imaging (DTI), which has been criticized for its partial volume effects in white matter regions containing complex crossing fibers (Alexander et al., 2001; Assaf and Pasternak, 2008). Consequently, tractography algorithms with improved ability to resolve white matter fibers in crossing regions, such as imaging analyses derived from diffusion spectrum imaging (DSI) (Wedeen et al., 2005), may provide a more sensitive measure of white matter microstructural disruptions.

The aim of this study was to investigate whether disruptions in white matter microstructures constitute a pathophysiological mechanism of hypertension-related cognitive detriments in older adults without dementia. Specifically, we first assessed the associations between hypertension status and performance in multiple cognitive domains and DSI-derived tract-specific white matter microstructural integrity, respectively, in a sample of cognitively intact older adults. We hypothesized that relative to normotensive older adults, hypertensive older adults would demonstrate poorer performance in multiple cognitive domains, including processing speed, executive function, and memory. We also hypothesized that hypertensive older adults would exhibit lower white matter microstructural integrity, particularly in long-range fiber bundles connecting the anterior and posterior brain regions. This study used a structural equation modeling (SEM) approach to evaluate the mediating effect of white matter microstructural integrity on the relationship between hypertension status and cognitive performance. The SEM approach enables the examination of theory-driven hypotheses about interrelation and directionality among multiple variables in a priori hybrid models (Kline, 2011), in addition to enabling the resolution of measurement errors in observed (manifest) variables that might otherwise diminish mediating relations in statistical analyses (MacKinnon, 2012), thus providing theoretical and statistical benefits. We further hypothesized that disrupted integrity of white matter microstructures would mediate the negative associations between hypertension and cognitive functions (i.e., processing speed, executive function, memory encoding, and memory retention).

2. Materials and methods

2.1. Participants

This study included a total of 66 cognitively normal older adults (age range: 50–85 years), consisting of 41 hypertensive (HTN) patients and 25 age-, education-, and sex-matched normotensive controls (NCs) recruited from local community through communication using flyers or word-of-mouth communication. The criteria for classifying participants as hypertensive were based on the guidelines of the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) (Chobanian et al., 2003): systolic blood pressure (SBP) of $\geq$140 mmHg, diastolic blood pressure (DBP) of $\geq$90 mmHg, and/or self-reported use of prescribed antihypertension medications. Blood pressure measurements were performed using an electronic sphygmomanometer (BM20 upper arm blood pressure monitor, Beurer GmbH, Germany) on the same day as the neuropsychological evaluation. SBP and DBP were measured as the mean of two seated blood pressure readings according to the standard protocols. Participants rested for at least 10 min in a chair with their feet on the floor and arms at heart level each time before blood pressure measurements. The two measurements were respectively taken in the beginning and near the end of the neuropsychological evaluation, with an average interval of 2–3 h. Measurements were performed by a licensed clinical neuropsychologist, who also conducted neuropsychological tests on each participant. The participants also participated in structured interviews, during which clinical information, including antihypertension medication usage, body mass index (BMI), self-reported history of chronic disease diagnoses (such as diabetes mellitus [DM] and cardiovascular diseases), and smoking status were recorded. In the hypertensive group, 46.3% of the participants took antihypertension medications. Because several studies (e.g., Bussel et al., 2016; J.-L. Hsu et al., 2012) have demonstrated DM to be associated with white matter microstructural abnormalities, history of DM diagnosis was also matched for the two groups. Individuals were excluded if they had any history of neurological or psychiatric disorders, substance abuse, or head injury accompanied by

disturbed consciousness; any evidence of visual and auditory problems precluding participation in neuropsychological testing; or contraindications to MRI (e.g., pacemaker or claustrophobia). This study was approved by the ethics committees and institutional review boards of both National Taiwan University Hospital and Taipei City Hospital, and written informed consent was obtained from all participants. Data will be made available on request. The demographic and clinical characteristics of the study population are presented in Table 1.

2.2. Neuropsychological evaluation

To evaluate participants' general cognitive functioning, all of them underwent a comprehensive neuropsychological battery assessing (1) processing speed, (2) executive function, and (3) learning and memory, which were the cognitive domains of interest in this study, as well as (4) attention and (5) language. Participants were defined as cognitively normal if they did not have more than one test score one standard deviation or more below the age-appropriate norm within a cognitive domain, in accordance with the recommendations of Jak et al. (2009). Neuropsychological evaluations were administered by a licensed clinical neuropsychologist. The average testing duration for each participant was approximately 2–3 h with short breaks in between. Cognitive tasks of a similar nature (e.g., memory related tasks) or stimulus (e.g., verbal materials) were staggered to minimize interference. For example, nonverbal tasks were arranged between immediate and delayed recall tasks in a verbal memory test, and vice versa. The following neuropsychological tests were employed. (1) Processing speed was assessed using the standardized Taiwanese version of the Digit Symbol Substitution Subtest of the Wechsler Adult Intelligence Scale, Third Edition (WAIS-3) (Chen and Chen, 2002), part 1 of the Color Trails Test (CTT_1) (D'Elia et al., 1996), and the word naming condition of the Stroop task (Stroop-w) (Golden, 1978). (2) Executive function was assessed using the Matrix Reasoning and Digit Span (backward length) subtests of WAIS-3, the color–word interference condition of the Stroop task (Stroop-cw), and the difference in time to completion between parts 2 and 1 of the CTT (CTT_{2-1}). (3) Learning and memory were assessed using the Verbal Paired Associates (VeP) and Visual Reproduction (VR) subtests of the Wechsler Memory Scale, Third Edition (WMS-3) (Hua et al., 2005), the Visual Paired Associates (ViP) subtest of the Wechsler Memory Scale, Revised (WMS-R) (Wechsler, 1987), and the California Verbal Learning Test, Second Edition (CVLT-II) (Delis, 2000). The immediate recall performances on the VeP and VR subtests of WMS-3, the ViP subtest of WMS-R, and List A total recall of CVLT-II were combined to form a measure of memory encoding. The delayed recall performances on the VeP and VR subtests of WMS-3, the delayed recall performance on the ViP subtest of WMS-R, and the long delayed free recall performance on CVLT-II were combined to form a measure of memory retention. Furthermore, (4) attention was assessed using the Digit Span (forward length) subtest of WAIS-3 and the Spatial Span (forward length) subtest of WMS-3. (5) Language was assessed using the Vocabulary subtest of WAIS-3 and the 30-item Boston Naming Test (Kaplan et al., 1983). In addition to cognitive measures, a self-report questionnaire based on the Geriatric Depression Scale (GDS) (Burke et al., 1991) was used to screen for depressive states among the study participants.

Composite indices of processing speed, executive function, memory encoding, and memory retention were generated using average standardized z-scores based on the current sample means and standard deviations of neuropsychological tests within each cognitive domain; higher scores indicated better performance. Given that the CTT outcomes were completion times (in seconds), with higher values representing poorer performance, the z-scores for CTT_1 and CTT_{2-1} were inverted to maintain a directionality consistent with the other measures.

Table 1
Group differences by hypertension status in demographic characteristics, clinical variables, and cognitive characteristics.

	HTN (n = 41) Mean (SD)	NC (n = 25) Mean (SD)	*t, F,* or χ^2 test	*P* value
Demographic Measures				
Age [years]	68.29 (7.29)	66.32 (5.12)	1.19	0.240
Education [years]	13.88 (2.57)	14.68 (2.45)	−1.25	0.215
Gender [Female/Male]	24/17	15/10	0.01	0.907
Clinical Measures				
GDS	3.54 (3.73)	2.36 (2.53)	1.39	0.169
DM [DM/non-DM]	8/33	1/24	3.17	0.075
SBP [mmHg]	146.73 (14.09)	121.56 (12.14)	7.41	<0.001*
DBP [mmHg)	83.80 (12.17)	71.00 (8.76)	4.58	<0.001*
HTN Medications [%]	46.3	0	16.27	<0.001*
BMI [kg/m^2]	24.00 (3.90)	22.20 (3.24)	1.94	0.057
Other VRFs	7/34	6/19	0.47	0.492
Smoking	2/39	0/25	1.26	0.262
Cognitive Functions				
Processing Speed [z]	−0.20 (0.79)	0.33 (0.62)	−2.86	0.006*
cov.			5.77	0.019*
Executive Function [z]	−0.19 (0.56)	0.32 (0.59)	−3.50	<0.001*
cov.			7.18	0.010*
Memory Encoding [z]	−0.16 (0.69)	0.26 (0.60)	−2.51	0.015*
Cov.			3.04	0.087
Memory Retention [z]	−0.13 (0.76)	0.21 (0.64)	−1.87	0.067
cov.			0.75	0.392

2.3. Imaging data acquisition and processing

2.3.1. MRI data acquisition

Imaging was performed on a 3T MRI system equipped with a 32-channel phased-array head coil and located at National Taiwan University Hospital. Axial scanning was performed with the slice orientation parallel to the anterior and posterior commissure plane, as determined on the sagittal localizer. High-resolution T1-weighted images were acquired using a three-dimensional magnetization–prepared rapid gradient echo (MPRAGE) sequence [repetition time (TR)/echo time (TE) = 2000 ms/2.98 ms; flip angle = 9°; field of view (FOV) = 256 × 256 × 192 mm^3; acquisition matrix = 256 × 256 × 192 mm^3; voxel size = 1 mm^3]. DSI (Wedeen et al., 2005) was performed using a single-shot spin-echo echo-planar imaging sequence [TR/TE = 9600 ms/130 ms; flip angle = 90°; FOV = 200 × 200 mm^2; acquisition matrix = 80 × 80 mm^2; slice thickness = 2.5 mm; slice number = 56; no gap] embedded with twice-refocused diffusion-sensitive gradients to minimize eddy current–induced geometric distortions (Reese et al., 2003). The sampling scheme comprised 102 diffusion-encoding directions pointing to grid points located in a half-sphere of diffusion-encoding space (q-space), with a maximum diffusion sensitivity (b_{max}) of 4000 s/mm^2 (Kuo et al., 2008). Neuroimaging data for all participants were collected within 3 months of the neuropsychological evaluation.

2.3.2. Diffusion imaging processing and analyses

The acquired 102 diffusion-attenuated signals from the half-sphere were projected to fill the sphere's other half for each voxel. The diffusion data of each voxel were transformed based on a three-dimensional Fourier formula to generate a probability density function (PDF). The second moment of the PDF along each of the 362 radial directions in a sixfold tessellated icosahedron was computed to obtain an orientation distribution function (ODF). The ODF was then decomposed into several constituent Gaussian ODFs using an iterative approach to derive local tract directions within each voxel (Yeh and Tseng, 2013). A scalar measure of the degree of diffusion directionality, namely generalized fractional anisotropy (GFA), was defined for each voxel as the ratio of the ODF standard deviation to its root mean square (Tuch, 2004). The mean

GFA (mGFA) value for each tract bundle is a DSI metric analogous to fractional anisotropy in DTI, reflecting the microstructural integrity of the white matter tract.

To examine the microstructural integrity of selected white matter tracts, tract-based automatic analysis (TBAA) was performed using the method developed by Chen et al. (2015). The executed TBAA reconstructed an entire brain white matter tract atlas comprising 74 bundles predefined on a high-quality DSI template, called NTU-DSI-122 (Hsu et al., 2015), by applying streamline-based deterministic tractography. A single study-specific template was created from the DSI data of all participants in the current study and then registered to NTU-DSI-122 to obtain the sampling coordinates. These coordinates were subsequently transformed to each individual participant's DSI data for sampling the mGFA value of each specific tract bundle. This study examined 14 specific white matter tract bundles that have been shown to be associated with hypertension (de Groot et al., 2015; Gons et al., 2012; Maillard et al., 2012; McEvoy et al., 2015; Salat et al., 2012; Suzuki et al., 2017); specifically, these tracts were the F*min*, F*maj*, bilateral IFOF, SLF, ILF, UF, CG*body*, and ATR. To limit the number of comparisons of group differences in white matter microstructural integrity, the mGFA value of SLF was obtained by combining SLF-I, SLF-II, and SLF-III; that of F*min* was obtained by combining the genu, dorsolateral prefrontal cortex, and ventrolateral prefrontal cortex parts of the corpus callosum; that of F*maj* was obtained by combining the precuneus and splenium parts of the corpus callosum, and that of ATR was obtained by combining thalamic radiation fibers connected to the ventrolateral and dorsolateral prefrontal cortices.

2.4. Statistical analyses

Group differences in demographic, clinical, and cognitive characteristics, and the microstructural integrity of white matter tracts were investigated using independent two-sample *t* tests or chi-square tests, as appropriate. Analysis of covariance (ANCOVA) tests were also conducted after age, sex, educational level, and DM status adjustments to investigate group differences in the composite cognitive indices and microstructural integrity of white matter tracts. Additionally, to investigate the potential confounding effect of antihypertensive medication usage, separate analyses were conducted within the hypertensive group to compare group differences between participants with untreated and treated hypertension in terms of demographics, clinical measures, cognitive characteristics, and white matter microstructural integrity by using two-sample *t* tests, chi-square tests, or ANCOVA tests. Only tracts demonstrating significant group differences by hypertension status in ANCOVA tests were included for further Pearson's zero-order correlation analysis using the four cognitive composite indices (i.e., processing speed, executive function, memory encoding, and memory retention). To achieve a balance between rigorous control of potential confounding covariates and the ability to detect meaningful findings, the conventional alpha level set at 0.05 was employed for examining group differences in demographic characteristics, clinical variables, cognitive characteristics, and microstructural integrity of the white matter tracts as well as the associations between white matter microstructural integrity and the cognitive composite indices. These analyses were performed using SPSS version 20.0 (IBM Corp., Armonk, NY). Effect sizes derived from Cohen's *d* values (for *t* tests) and Cohen's *f* values (for *F* tests) (Cohen, 1988) were calculated for significant between-group differences in cognitive and white matter variables using G*Power version 3.1 (Faul et al., 2009).

To examine the mediating effects of white matter microstructural integrity on the relationship between hypertension status and the four cognitive composite indices, SEM analyses were performed for each cognitive domain. This study followed the recommendations of Hayes (2013) and Zhao et al. (2010) in defining mediating effects; according to these recommendations, the only key requirement for demonstrating a mediating effect is the presence of a significant indirect effect (defined as the product of the direct paths). White matter tract mGFA values significantly associated with both hypertension status and the cognitive composite index were specified as latent mediating variables for the hypothesized mediation model of each cognitive composite index. Hypertension status was coded as a dummy independent variable (1 = hypertensive; 0 = normotensive control) in each mediation model. All SEM coefficients were evaluated using maximum likelihood estimation and bias-corrected 95% confidence intervals (95% CI_{BC}) generated from a bootstrap resampling procedure with 5000 draws (Hayes, 2013; Zhao et al., 2010). Mediation is present if the 95% CI_{BC} for the indirect effect does not contain a zero value. SEM model fitness was evaluated using the following commonly used indices. A model was considered to have a satisfactory fit if it exhibits a normed chi-square (χ^2/df) value of $\leq$2.0 (Hooper et al., 2008; Mueller, 1999; Tabachnick and Fidell, 2007), goodness-of-fit index (GFI) of $\geq$0.90 (Hooper et al., 2008), comparative fit index (CFI) of $\geq$0.95 (Hu and Bentler, 1999), Tucker–Lewis index (TLI) of $\geq$0.95 (Hu and Bentler, 1999), and root mean square error of approximation (RMSEA) of <0.09 (Chen et al., 2008). Notably, scholars have proposed that RMSEA values between 0.08 and 0.10 indicate a reasonable fit and those of <0.08 indicate a good fit (Hooper et al., 2008; MacCallum et al., 1996). However, we adopted an adjusted cutoff criterion of RMSEA < 0.09, derived from interpolation based on a power curve under the correct specification condition of a simulation research proposed by Chen et al. (2008); we adopted this criterion because the upward bias of the RMSEA is liable to over-reject appropriate models in a small sample such as the one in this study (Bentler and Yuan, 1999; Chen et al., 2008; Hu and Bentler, 1999). Modification indices were examined for models with a fitness that was less reasonable, and where theoretically justified, residuals of homologous tracts were specified to correlate with each other in the evaluation of the proposed mediating model. All SEM analyses were performed using Amos version 24.0 (IBM SPSS, Chicago, USA).

3. Results

3.1. Demographic, clinical, and cognitive characteristics

The demographic, clinical, and cognitive characteristics of the study groups are shown in Table 1. The two groups were well matched by age, level of education, sex, DM history, BMI, vascular risk factors other than hypertension, smoking status, and GDS score ($P > 0.05$ for all). As expected, the mean SBP ($t_{(64)} = 7.41$, $P < 0.001$) and DBP ($t_{(64)} = 4.58$, $P < 0.001$), and the percentage of antihypertension medication consumption ($\chi^2_{(1)} = 16.27$, $P < 0.001$) were significantly higher in the hypertensive group than in the NC group.

Regarding the results of independent two-sample *t* tests, the hypertensive group demonstrated significantly poorer performance on the composite indices of processing speed ($t_{(64)} = -2.86$, $P = 0.006$, Cohen's $d = 0.69$), executive function ($t_{(64)} = -3.50$, $P < 0.001$, Cohen's $d = 0.81$), and memory encoding ($t_{(64)} = -2.51$, $P = 0.015$, Cohen's $d = 0.61$) compared with the NC group (Table 1). In addition, the hypertensive group tended toward poorer performance on the composite index of memory retention ($t_{(64)} = -1.87$, $P = 0.067$, Cohen's $d = 0.46$). When statistically controlling for age, sex, educational level, and DM status, group differences by hypertension status in cognitive characteristics all diminished to some extent, but the hypertensive group still exhibited significantly poorer performance on the composite indices of processing speed ($F_{(1, 60)} = 5.77$, $P = 0.019$, Cohen's $f = 0.31$) and executive function ($F_{(1, 60)} = 7.18$, $P = 0.010$, Cohen's $f = 0.35$), as well as a trend to poorer performance on the composite index of memory encoding ($F_{(1, 60)} = 3.04$, $P = 0.087$, Cohen's $f = 0.22$) compared to the NC group. The performance levels of the study population on each individual neuropsychological measure of the four cognitive domains are presented in Supplementary Table 1.

Additionally, separate analyses were conducted for the two subgroups (i.e., treated vs. untreated participants) of the hypertensive group in terms of cognitive performance. The results revealed that the participants

with untreated and treated hypertension did not differ in any cognitive composite indices ($P > 0.05$ for all; Supplementary Table 2).

Note: Signficant differences at the $P < 0.05$ threshold are indicated by an asterisk (*). Comparisons of categorical demographic and clinical variables were performed by means of chi-square tests. Results of group differences in cognitive functions analyzed by ANCOVA tests with age, sex, educational level, and DM status as covariates are shown in the rows of *cov*. Abbreviations: HTN, hypertension; NC, normotensive control; SBP, systolic blood pressure; DBP, diastolic blood pressure; HTN medications, use of antihypertension medications; DM, diabetes mellitus; GDS, Geriatric Depression Scale; BMI, body mass index; other VRFs, vascular risk factors other than HTN (composed of cardiovascular diseases, atrial fibrillation, and left ventricular hypertrophy); *cov.*, covariates.

3.2. Group differences in white matter tract microstructural integrity

The results of the independent two-sample *t* tests revealed that the hypertensive group demonstrated significantly lower mGFA values in the left IFOF ($t(64) = -3.74$, $P = 0.000395$, Cohen's $d = 0.87$), right IFOF ($t(64) = -3.03$, $P = 0.004$, Cohen's $d = 0.73$), left ILF ($t(64) = -3.49$, $P = 0.001$, Cohen's $d = 0.82$), right SLF ($t(64) = -2.46$, $P = 0.017$, Cohen's $d = 0.60$), left ATR ($t(64) = -3.01$, $P = 0.004$, Cohen's $d = 0.72$), right ATR ($t(64) = -2.81$, $P = 0.007$, Cohen's $d = 0.68$), and F*min* ($t(64) = -2.20$, $P = 0.031$, Cohen's $d = 0.54$) compared with the NC group (Supplementary Table 3). Group differences in terms of the other white matter tract bundles (i.e., left SLF, right ILF, bilateral UF, bilateral CG*body*, and F*maj*) did not achieve statistical significance. After adjustments of age, sex, educational level, and DM status, the hypertensive group still had significantly lower mGFA values in the left IFOF ($F_{(1, 60)} = 9.21$, $P = 0.004$, Cohen's $f = 0.39$), right IFOF ($F_{(1, 60)} = 5.80$, $P = 0.019$, Cohen's $f = 0.31$), left ILF ($F_{(1, 60)} = 8.08$, $P = 0.006$, Cohen's $f = 0.37$), right SLF ($F_{(1, 60)} = 5.84$, $P = 0.019$, Cohen's $f = 0.31$), left ATR ($F_{(1, 60)} = 9.30$, $P = 0.003$, Cohen's $f = 0.39$), and right ATR ($F_{(1, 60)} = 8.21$, $P = 0.006$, Cohen's $f = 0.37$) compared with the NC group (Fig. 1 and Supplementary Table 3), while group differences in F*min* ($F(1, 60) = 2.75$, $P = 0.103$, Cohen's $f = 0.21$) diminished to a marginal level. The hypertensive group also had marginally significantly lower mGFA values in the left SLF ($F_{(1, 60)} = 3.05$, $P = 0.086$, Cohen's $f = 0.23$) compared with the NC group when covariates were accounted for. Group differences in terms of the other white matter tract bundles (i.e., right ILF, bilateral UF, bilateral CG*body*, and F*maj*) still had a nonsignificant pattern (Supplementary Table 3). Additionally, separate analyses were performed for the two subgroups (i.e., treated vs. untreated participants) of the hypertensive group in terms of white matter variables. The results revealed that the participants with untreated and treated hypertension had comparable mGFA values across all investigated white matter tract bundles (all *P values* > 0.05; Supplementary Table 2).

3.3. Associations between white matter tract integrity and cognitive composite indices

Significant group differences observed in white matter tracts according to hypertension status in ANCOVA tests (i.e., bilateral IFOF, left ILF, right SLF, and bilateral ATR) were included in further correlation analyses with the four composite cognitive indices (i.e., processing speed, executive function, memory encoding, and memory retention). As shown in Table 2, the composite index of processing speed was significantly associated with mGFA values in the bilateral IFOF, left ILF, and bilateral ATR tracts. Moreover, the composite indices of executive function, memory encoding, and memory retention were significantly associated with mGFA values in the bilateral IFOF tracts.

Note: Significant associations at the $P < 0.05$ threshold are indicated by an asterisk (*). Abbreviations: *l*-IFOF/*r*-IFOF, left/right inferior frontal-occipital fasciculus; *l*-ILF, left inferior longitudinal fasciculus; *r*-SLF, right superior longitudinal fasciculus; *l*-ATR/*r*-ATR, left/right anterior thalamic radiations.

3.4. Mediating effects of white matter tract integrity on relationships between hypertension status and cognitive performance

SEM analyses were conducted to examine the mediating effects of white matter tract microstructural integrity on the relationships between hypertension and performance in the four cognitive domains. Tracts demonstrating significant relationships with both hypertension status and the cognitive composite index were specified as constituting a mediating factor for each cognitive domain. Specifically, bilateral IFOF, left ILF, and bilateral ATR together were specified as one mediating factor for the proposed model of processing speed; additionally, bilateral IFOF were specified as the mediating factor for the proposed models of executive function, memory encoding, and memory retention.

Note: Signficant indirect effects at the $P < 0.05$ threshold are indicated by an asterisk (*). Abbreviations: χ^2/df, normed chi-square; GFI, goodness-of-fit index; CFI, comparative fit index; TLI, Tucker–Lewis index; RMSEA, root mean square error of approximation.

As shown in Table 3, all four proposed mediating models had satisfactory model fit indices, and the estimated indirect effect of each model reached statistical significance; these results demonstrate the mediating effects of white matter microstructural integrity across each cognitive domain, consistent with the recommendations of Hayes (2013) and Zhao et al. (2010). For the composite index of processing speed, the negative association with hypertension was mediated through the white matter integrity of the left and right IFOF, left ILF, and left and right ATR fiber bundles. For the other three cognitive composite indices (i.e., executive function, memory encoding, and memory retention), the negative association with hypertension was mediated through the white matter integrity of bilateral IFOF fiber bundles. Notably, concerning the mediating effects of white matter integrity, the direct effects of hypertension on processing speed (standardized coefficient = −0.14, $P = 0.148$), memory encoding (standardized coefficient = −0.17, $P = 0.122$), and memory retention (standardized coefficient = −0.08, $P = 0.538$) were not significant [Fig. 2 (a), (c), and (d); Supplementary Table 4], suggesting that the microstructural integrity of the selected white matter tracts fully mediated the relationship between hypertension and the three domains of cognitive function. Specifically, the presence of a hypertension diagnosis contributed to z-score reductions of 0.19 (= -0.43×0.45) in processing speed, 0.13 (= -0.38×0.33) in memory encoding, and 0.15 (= -0.39×0.39) in memory retention, completely contingent on the disrupted integrity of the selected white matter tracts. By contrast, the direct effect of hypertension on executive function (standardized coefficient = −0.32, $P = 0.004$) remained significant [Fig. 2 (b) and Supplementary Table 4], indicating a partial mediating effect, in which the presence of a hypertension diagnosis contributed to a z-score reduction of 0.09 (= -0.38×0.22) in executive function, partly contingent on the disrupted integrity of the selected white matter tracts.

4. Discussion

By employing a comprehensive neuropsychological assessment battery linked to various cognitive domains and an advanced TBAA derived from DSI, this study clarified the role of white matter microstructural disruptions in hypertension-related cognitive detriments by applying an SEM multivariate analysis approach. The results reveal that hypertensive older adults demonstrated poorer performance on processing speed, executive function, and memory encoding, accompanied by a tendency toward poor memory retention, compared to the older adults without hypertension. In addition, we observe reduced white matter microstructural integrity related to hypertension, particularly in long-range fiber bundles connecting anterior brain regions with posterior brain regions. In line with our hypothesis, the disrupted microstructural integrity of specific long-range fiber bundles substantially mediated the negative relationships between hypertension and processing speed, executive

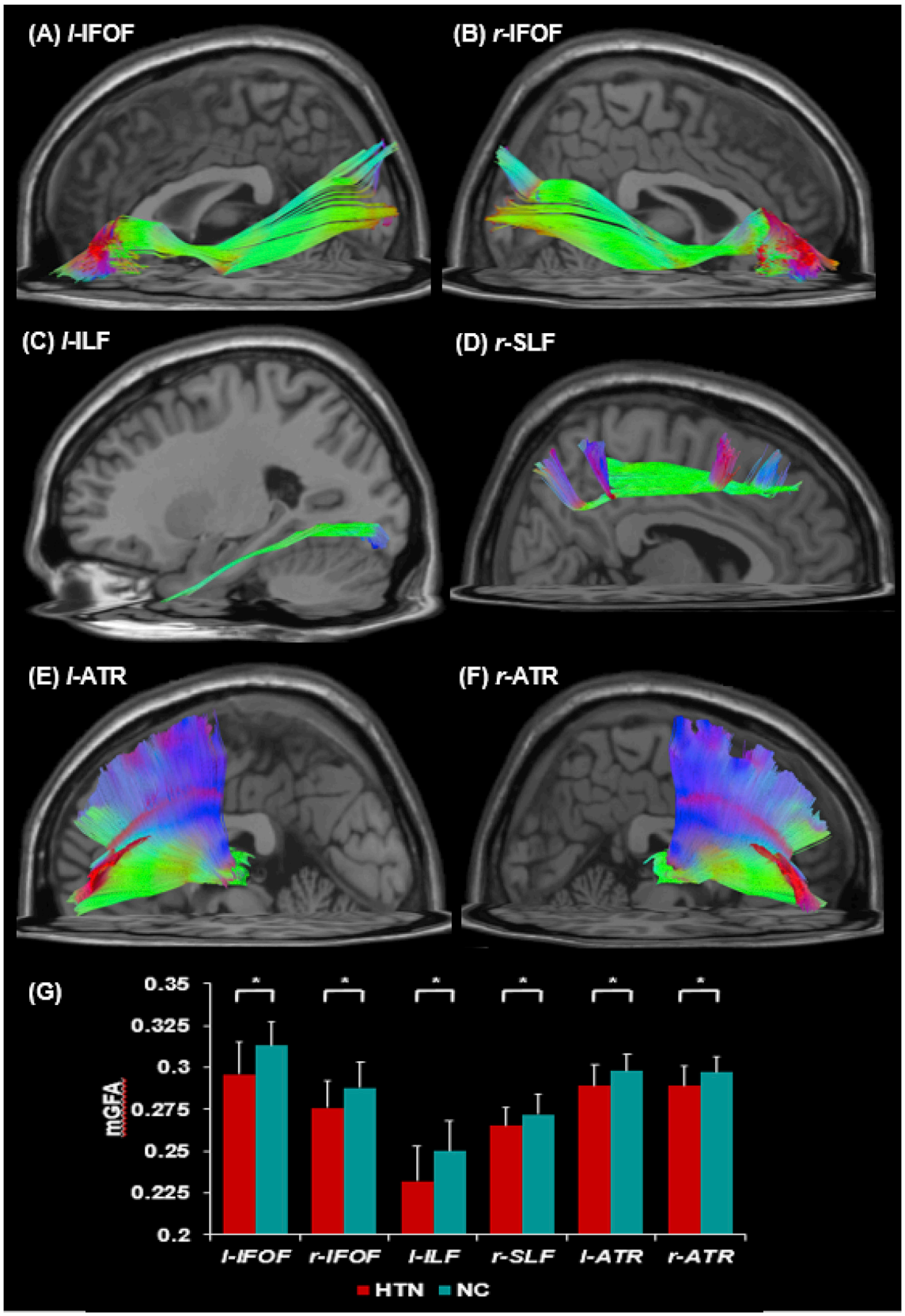

Fig. 1. Diffusion spectrum imaging (DSI) maps and bar chart of the six white matter tracts showing significant group differences by hypertension status with statistically controlling for age, sex, educational level, and DM status. DSI maps: (A) left IFOF, (B) right IFOF, (C) left ILF, (D) right SLF, (E) left ATR, and (F) right ATR. (G) Bar chart. Bars and error bars denote the mean and standard deviation, respectively, of the mGFA value for each white matter tract within each group. Abbreviations: HTN, hypertension; NC, normotensive control; mGFA, mean generalized fractional anisotropy; *l*-IFOF/*r*-IFOF, left/right inferior frontal-occipital fasciculus; *l*-ILF, left inferior longitudinal fasciculus; *r*-SLF, right superior longitudinal fasciculus; *l*-ATR/*r*-ATR, left/right anterior thalamic radiations. * denotes a value significant at $P < 0.05$ threshold.

Table 2
Associations between white matter microstructural integrity in tracts showing significant group differences by hypertension status and cognitive composite indices.

	Processing Speed		Executive Function		Memory Encoding		Memory Retention	
	r	*P* value	*r*	*P* value	*r*	*P* value	*r*	*P* value
l-IFOF	0.53	<0.001*	0.35	0.004*	0.41	0.001*	0.44	<0.001*
r-IFOF	0.46	<0.001*	0.25	0.047*	0.30	0.015*	0.33	0.007*
l-ILF	0.31	0.012*	0.20	0.113	0.24	0.051	0.20	0.113
r-SLF	−0.02	0.864	−0.06	0.660	0.05	0.701	0.13	0.284
l-ATR	0.27	0.030*	0.14	0.263	0.11	0.389	0.14	0.257
r-ATR	0.27	0.026*	0.14	0.258	0.15	0.216	0.22	0.079

Table 3
Mediating effects: evaluation of model fit indices and estimation of indirect effects.

Model	χ^2	*df*	χ^2/df	GFI	CFI	TLI	RMSEA	Indirect Effect Std. estimate [95% CI_{BC}]	*P* value
Processing Speed	12.459	12	1.038	0.950	0.999	0.997	0.024	−0.19 [-0.34, −0.08]	0.001*
Executive Function	0.696	1	0.696	0.995	1.000	1.014	0.000	−0.09 [-0.20, −0.01]	0.038*
Memory Encoding	0.555	1	0.555	0.996	1.000	1.020	0.000	−0.13 [-0.24, −0.05]	0.004*
Memory Retention	0.278	1	0.278	0.998	1.000	1.033	0.000	−0.15 [-0.26, −0.07]	0.001*

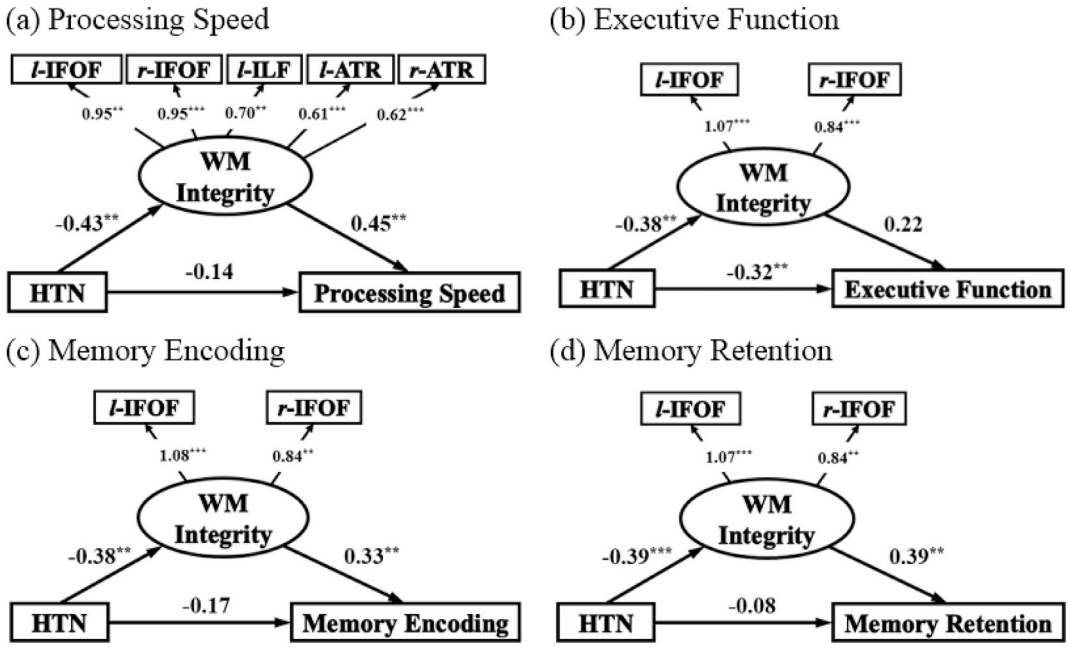

Fig. 2. Models of the mediating effect of white matter microstructural integrity on the relationship between hypertension and cognitive function. Mediation models for (a) processing speed, (b) executive function, (c) memory encoding, and (d) memory retention. Note: Values shown are standardized coefficients. $^*P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$. Abbreviations: HTN, hypertension; WM Integrity, white matter microstructural integrity; *l*-IFOF/*r*-IFOF, left/right inferior frontal-occipital fasciculus; *l*-ILF, left inferior longitudinal fasciculus; *l*-ATR/*r*-ATR, left/right anterior thalamic radiations.

function, memory encoding, and memory retention, even in cognitively intact older adults. This study demonstrates for the first time that disruptions in white matter microstructures lay the foundations for multiple hypertension-induced detriments in cognitive function.

4.1. Pattern of cognitive detriments related to hypertension and white matter disruptions

Overall, our results indicating the adverse relationship between hypertension and cognitive function are consistent with those of other studies that have investigated hypertension-related cognitive detriments (e.g., Brady et al., 2005; Bucur and Madden, 2010; de Moraes et al., 2002; Hannesdottir et al., 2009; Saxby et al., 2003); additionally, our results could corroborate the evidence of hypertension-related cerebral white matter pathology derived from numerous studies (e.g., de Groot et al., 2015; Maillard et al., 2012; McEvoy et al., 2015; Suzuki et al., 2017). As expected, hypertensive older adults exhibited poorer performance on multiple cognitive domains and reduced microstructural integrity, particularly in long-range fiber bundles, both of which are consistent with the suggestions of previous studies regarding the vulnerability of periventricular white matter areas to the adverse effects of hypertension (Henskens et al., 2009; Raz et al., 2007; Yoshita et al., 2006). Specifically, hypertension-related pathologic abnormalities in periventricular areas primarily disrupt long-range fiber bundles that connect anterior brain regions with spatially distant posterior cortical areas and subcortical nuclei; therefore, such disruptions are believed to lead to cognitive detriments in multiple domains (Bolandzadeh et al., 2012; Smith et al., 2011; Tzourio et al., 2014). Notably, the extent of such detriments observed in this study appeared more pronounced for executive function and processing speed than for memory encoding and especially memory retention. Such a pattern was consistent with those in other studies (Iadecola et al., 2016) and was stable regardless of whether confounding

covariates (i.e., age, sex, education level, and DM status) were considered in the analyses. One possible explanation for the marginal association of hypertension on memory retention is that our relatively small sample size precluded detection of a significant association on this cognitive domain. Alternatively, the varying extents of association between hypertension and the four cognitive functions could be partially explained by the hypothesis of frontal vulnerability to hypertension (Brady et al., 2005; Bucur and Madden, 2010; Raz et al., 2003), according to which hypertension preferentially undermines the structural and functional integrity of prefrontal regions, which in turn impairs those cognitive processes (e.g., executive function, processing speed, and memory encoding) largely served by prefrontal and associated substrates. In addition, some studies examining hypertension-related white matter microstructural disruptions have indicated an anterior-to-posterior gradient of long-range fiber bundles (de Groot et al., 2015; McEvoy et al., 2015; Salat et al., 2012). Specifically, they have demonstrated that the adverse effect of hypertension, although widespread across the brain, is apparently more prominent for anterior fiber bundles such as those in frontal areas and less prominent for posteriorly situated fiber bundles such as those in the medial temporal and occipital areas. This study's finding of a disproportionate association of hypertension with the four cognitive functions is also partly in agreement with this anterior-to-posterior gradient of hypertension-related white matter pathologic changes.

4.2. Possible pathophysiological mechanisms underlying white matter disruptions related to hypertension

In agreement with the presumed vulnerability of periventricular white matter areas and the anterior-to-posterior gradient of long-range fiber bundles to hypertension, this study found that hypertensive older adults exhibited significantly diminished microstructural integrity in long-range white matter tracts connecting anterior to posterior cerebral regions, including the bilateral IFOF (connecting the frontal and occipital regions), left ILF (connecting the temporal and occipital regions), right SLF (connecting the frontal and parietal regions), and bilateral ATR (connecting the frontal regions to the thalamic nuclei). Additionally, the findings on other tracts such as the left SLF and forceps minor (connecting the bilateral homologous frontal regions)—but not the forceps major (connecting the bilateral homologous occipital regions)—demonstrate marginal significance, which is also consistent with the anterior-to-posterior pattern. These findings are likely explained by the outside-in vasculature arrangement of brain vessels that produces a white matter watershed extending by 3–13 mm from the ventricular spaces (Moody et al., 1990). This periventricular white matter watershed irrigated by nonoverlapping vascular territories of distal arterioles is considered to be liable to hypoperfusion, the major deleterious effect of hypertension (Iadecola, 2013; Tzourio et al., 2014). Although the pathophysiological mechanisms underlying the relationships between hypertension-related hypoperfusion and white matter pathology are not yet fully understood, the mechanical stress imposed by hypertension might induce histological changes in the cerebral small vessels, such as arteriolosclerosis and lipohyalinosis, which likely result in hemodynamic responses that are uncoordinated with neural activation or even neurovascular unit decoupling, subsequently disrupting cerebral blood flow autoregulation and the trophic and metabolic supply to the white matter tissues (Iadecola, 2013; Pantoni, 2010; Pantoni and Garcia, 1997; Tzourio et al., 2014). Accordingly, long-range fiber bundles that traverse the less-irrigated periventricular watershed are particularly susceptible to pathologic alterations (Bolandzadeh et al., 2012; Smith et al., 2011). In accordance with this pathogenic mechanism, the long-range fiber tracts determined to be relevant in this study (e.g., IFOF, ILF, ATR, SLF, and forceps minor) all pass alongside the lateral ventricles to a large extent (Catani et al. 2002, 2003; Caverzasi et al., 2014; Jang and Yeo, 2013; Makris et al., 2004; Martino et al., 2010; Sarubbo et al., 2013; Wu et al., 2016). Additionally, the vulnerability to hypertension of long-range association fiber bundles observed in this study generally corresponds to the proposed "last-in, first-out" trend of white matter degradation (Bennett and Madden, 2014; Raz, 2000), wherein association fibers, which complete myelination later during neural development (Leipsic, 1901), tend to be the first to be affected by aging or pathologic processes (Stadlbauer et al., 2008; Sullivan and Pfefferbaum, 2006). Furthermore, our findings on hypertension-related cognitive detriments and white matter microstructural disruptions also concur with the "disconnection hypothesis," according to which pathologic changes in white matter structure interfere with communication among neural networks, consequently inducing cognitive decline (Hogan et al., 2006). However, in contrast to some findings of previous studies (de Groot et al., 2015; Gons et al., 2012; Maillard et al., 2012; McEvoy et al., 2015; Suzuki et al., 2017), the present study did not observe significant negative associations between hypertension and the left SLF, right ILF, bilateral UF, bilateral CG*body*, forceps minor, and forceps major. This discrepancy may be due primarily to differences in methodology. Specifically, the present study used DSI to overcome the limitations of DTI used in previous studies. The present study also adopted a relatively rigorous control for various covariates (i.e., age, sex, educational level, and DM status) when group differences were compared regarding white matter microstructural integrity, which likely minimized potential confounding factors that were not controlled in related studies (de Groot et al., 2015). Furthermore, our sample was more likely to have excluded individuals with mild cognitive impairment than samples in previous studies because we used a relatively comprehensive neuropsychological test battery and classification criteria to define cognitive intactness. All of these methodological differences might account for our more restricted findings on hypertension-related reduction of white matter microstructural integrity.

4.3. Mediating role of the IFOF in multiple cognitive domains

Among various fiber bundles showing significant hypertension-related microstructural disruptions, we identified specific white matter fiber bundles that actually mediate the adverse relationships between hypertension and each of the four cognitive functions. For processing speed, our results demonstrate that hypertension negatively related to this cognitive function through numerous white matter fiber bundles, including the bilateral IFOF, left ILF, and bilateral ATR. The observed relationships between processing speed and each of the five white matter fiber bundles examined in this study are consistent with the findings of other studies that have investigated white matter tracts correlated with processing speed deficits (Cremers et al., 2016; Duering et al. 2011, 2013, 2014; Latini, 2015; Latini et al., 2017; Turken et al., 2008; Voineskos et al., 2012). Notably, the associations of hypertension with executive function, memory encoding, and memory retention were all significantly mediated through the integrity of the bilateral IFOF. Several studies (Caverzasi et al., 2014; Panesar et al., 2017; Sarubbo et al., 2013; Wu et al., 2016) employing postmortem fiber dissection and in vivo diffusion imaging techniques have demonstrated that the IFOF represent a set of widespread long-range association bundles spanning from the frontal regions (including the superior frontal, middle frontal, inferior frontal, dorsolateral prefrontal, and orbitofrontal cortices) to distributed posterior cerebral regions (possibly involving the superior parietal, temporal–basal, and occipital–extrastriate areas). Accordingly, the IFOF have been proposed to constitute a "multifunction white matter bundle" (Sarubbo et al., 2013; Wu et al., 2016) that may subserve cognitive performance on processing speed, executive function, learning and memory, language, and visuospatial abilities. Studies examining tract-specific links between white matter structures and cognitive detriments have shown that the IFOF are probably the white matter bundle most consistently and prominently associated with general cognitive decline, especially in processing speed and executive function, although less in learning and memory (Cremers et al., 2016; Perry et al., 2009; Santiago et al., 2015). One study reported a mediating effect of global connectivity efficiency in the frontal and parietal white matter networks on executive function in hypertension (Li et al., 2016), which is

consistent with our findings regarding tract-specific mediating effects of the IFOF—a fiber bundle connecting frontal to posterior cerebral regions, including the parietal lobe—on executive function. However, our study extends the findings of Li et al. on executive dysfunction associated with hypertension-related regional white matter disruptions; in other words, our study revealed the strategic role of the IFOF in other cognitive domains including processing speed, memory encoding, and memory retention, thus also providing supporting evidence for the notion of the IFOF as a multifunction white matter bundle (Sarubbo et al., 2013; Wu et al., 2016).

4.4. Limitations, strengths, and future directions

Some possible limitations in the current study should be considered. First, specific characteristics of hypertension, such as use of antihypertension medications, medication type, and hypertension duration, were not considered in the statistical analyses. Although this remains controversial, these characteristics of hypertension might moderate the progression of brain lesions and consequent cognitive dysfunctions (Tzourio et al., 2014; Williamson, 2018). For example, one recent large-scale randomized clinical trial had preliminary success in lowering the risk of cognitive decline through the intensive treatment of hypertension (Williamson, 2018). Other evidence also suggest that there seems to be an age-dependent effect of hypertension exposure, whereby midlife onset hypertension contributes to brain lesions and cognitive impairment, while late-life onset hypertension might protect against them (Tzourio et al., 2014). Although the interrelationships between the demographic and clinical variables require further investigation, the finding that no target outcome variables were significantly different between untreated and treated hypertensive participants in this study may at least support our finding that hypertension-related detriments were not exacerbated in untreated patients with hypertension. Nevertheless, obtaining precise information related to these clinical characteristics represented a practical challenge, because many of the participants were uncertain of their onset time and kept no record of their hypertension medication use. A prospective study design would best address these shortcomings. In addition, the current study followed the conventional JNC 7 guidelines (Chobanian et al., 2003) in classifying hypertension status rather than the updated JNC 8 guidelines (James et al., 2014), which did not redefine the hypertension classification criteria established in JNC 7 but suggested a higher threshold for initiating pharmacologic treatment for hypertensive person aged 60 years or older compared to the JNC 7 guidelines. In contrast, the 2017 American College of Cardiology/American Heart Association (ACC/AHA) Clinical Practice Guidelines for High Blood Pressure in Adults (Whelton et al., 2018) proposed lower cut-off levels of blood pressure to diagnose and treat hypertension compared to the JNC 7 guidelines; however, such change has raised controversy over possible negative effects related to the treatment that initiates too early for some people whose blood pressures are just above the cut-off levels (Bell et al., 2018; Poulter et al., 2018). Future work to examine the long term effect of hypertension in accordance with the latest guidelines, such as the treatment parameters, on cognitive function and brain variables are essential. Second, this study drew inferences about the pathophysiological mechanisms of hypertension-related microstructural disruptions mainly from the perspective of vasculature arrangement and its relation to hypertension-related cerebral hypoperfusion because of the nature of the imaging data collected. Examinations of other potential hemodynamic pathophysiological mechanisms in the relationships between hypertension and white matter pathology, such as hypertension-induced cerebral arteriole remodeling or arteriolosclerosis, neurovascular unit decoupling, and subsequent disrupted cerebral blood flow regulation (Iadecola, 2013; Pantoni, 2010; Pantoni and Garcia, 1997; Tzourio et al., 2014), would require a combination of diffusion and perfusion neuroimaging techniques for further elucidation and verification. Third, this study's relatively small sample size might have hindered the generalization capacity of the findings, and it also precluded us from examining interrelationships among the four cognitive domains and constructing a complex hybrid model containing excessive observed variables. Notably, we conducted an a priori sample size analysis based on the results of Li and colleagues' (2016) study to estimate the required sample size for this study and the analysis suggested a required sample size of 52 in order to achieve an adequate power of 0.8. We also conducted a sensitivity analysis to estimate the required effect size for achieving an adequate power of 0.8 with the current sample size of 66, and the result revealed a required effect size of Cohen's *f* of 0.35, which was exactly comparable to the mean effect size derived from the results of significant group differences in this study. The converging results demonstrated that our study achieved an adequate level of power and effect size with its sample size. The satisfactory model fitness and the stable estimated parameters of the SEM results also indicate that the study findings are convincing. Compared with other relevant studies, the present study used a more stringent inclusion criterion concerning objective cognitive function than other studies (−1 SD or higher rather than −1.5 SD or higher) to rule out individuals with mild cognitive impairment, and this study also matched multiple potentially confounding background variables (such as age, sex, education, and diabetes mellitus history). The efforts taken to minimize confounding in sampling limited our final attainable sample size to some extent. However, potential confounding from neurodegenerative processes or other pathological mechanisms were more likely to be minimized. The cross-sectional nature of this study might limit our ability to make causal inferences in terms of the deleterious effects that hypertension may exert on either brain integrity or cognitive functions. The results regarding the observed pathophysiological mechanisms require further validation by studies with a longitudinal design. Nevertheless, all the proposed mediation models in the current study exhibited relatively satisfactory model fit indices and stable estimated coefficients, suggesting that the mediating effects were robust.

This study also has several noteworthy strengths. First, adequate and representative neuropsychological tests were used to explore and comprehensively investigate several targeted cognitive domains particularly associated with hypertension. Second, strict criteria for defining participants' cognitive status were adopted to reduce confounding variables and enhance the generalizability of the study findings. To our knowledge, none of the relevant prior studies examining the relationship between hypertension-related white matter disruption and cognition have ever taken such stringent inclusion criteria as we did. Moreover, a tract-specific tractography technique was employed together with an advanced diffusion imaging technique (i.e., DSI) to enable precise construction and location of strategic white matter fiber bundles. Our literature review shows that, hitherto, there have been no relevant studies that established the mediating role of white matter microstructures in such multiple hypertension-associated cognitive domains and precisely specified the cardinal set of white matter tracts that take part in the pathophysiological mechanism. The present study is distinguished from the prior studies in that, through the utilization of the DSI-derived tract-specific approach and the SEM approach, we, for the first time, manifested the IFOF as a remarkable multifunction white matter bundle relating hypertension to multiple cognitive detriments.

5. Conclusion

In conclusion, the findings of this study elucidate the potential pathophysiological mechanism underlying the relationships between hypertension and cognitive detriments. To our knowledge, this is the first study to suggest that hypertension may negatively relate to multiple cognitive functions (i.e., processing speed, executive function, memory encoding, and memory retention) by undermining the microstructural integrity of specific white matter fiber bundles, even for older adults that have a normal cognitive status based on demographically corrected norms. This study is also the first to identify strategic long-range white matter fiber bundles that provide a bridge between

hypertension and cognitive detriments, especially highlighting the role of a multifunction white matter bundle widely distributed from the frontal to posterior cerebral regions as a pivotal mediator. Overall, our findings indicate the necessity of vascular health maintenance and early intervention against vascular risk factors to safeguard brain integrity and prevent cognitive decline in later life. Future research with a larger sample size and longitudinal follow-up is required to replicate and validate this study and further elucidate the interrelationships among vascular factors, white matter microstructural integrity, and multiple cognitive functions.

Conflicts of interest

Declarations of interest: none.

Acknowledgments

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.neuroimage.2019.04.063.

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