



Characteristic changes in the default mode network in hypertensive patients with cognitive impairment

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Abstract

Hypertension has a close affinity to brain degeneration and cognitive decline during the aging process. The default mode network (DMN) is usually affected in various diseases related to cognitive impairment (CI). The present research aimed to explore the alterations in the DMN and its subcomponents in hypertensive patients with and without CI and to investigate the associations between cognitive performance and network abnormalities. Resting-state functional magnetic resonance imaging and neuropsychological tests were performed in 74 subjects, namely, 30 hypertensive patients with normal cognition (HTN-NC), 25 hypertensive patients with CI (HTN-CI), and 19 healthy controls. Seed-based functional connectivity (FC) analysis was performed to identify the DMN patterns. The group differences in the DMN were mainly shown in brain regions related to the core subsystem and the dorsal medial subsystem of the DMN. Post hoc analysis revealed a trend of dissociation among the DMN subsystems in the HTN-NC group. In contrast, the HTN-CI group displayed extensively increased FC in both subsystems. Importantly, increased FC of the dorsal medial subsystem in the HTN-CI patients was associated with poor cognitive performance, such as scores on Mini-Mental State Examination ($\rho = -0.438$, $P = 0.029$) and Montreal Cognitive Assessment ($\rho = -0.449$, $P = 0.025$). The findings suggest that extensively increased connectivities in the core subsystem and the dorsal media subsystem of the DMN may distinguish hypertension with CI from hypertension with normal cognition. The characteristic change in the dorsal medial subsystem may become an early imaging biomarker for the diagnosis and treatment of cognitive impairment associated with hypertension.

Keywords cognition · default mode network · functional connectivity · hypertension · resting state

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Introduction

Hypertension remains a worldwide public health problem due to its high prevalence. In China, hypertension accounted for nearly 1/3 of the total deaths and ~1/6 of the total disability-adjusted life years in 2013, mainly because of its contributions to cardio-cerebral vascular diseases [1]. Furthermore, hypertension can act as an independent risk factor in the development of cognitive decline, Alzheimer's disease (AD), and vascular dementia [2–4].

White matter (WM) lesions are commonly observed in hypertensive patients [5], and these lesions are supposed to disrupt the inner links of brain structures, leading to cognitive impairment. Brain atrophy [6] and cerebral amyloid β -protein deposition [7] are also associated with hypertension. The imbalance of cerebral blood flow perfusion in the frontal and parietal lobes [8–10] may be another cause of hypertension-related cognitive impairment. However, the mechanisms underlying the

development of cognitive impairment in hypertension remain relatively unclear, and predicting cognitive impairment in hypertensive patients is still difficult.

A series of functional resting-state networks (RSNs) have been identified based on the temporal correlations between fluctuations in blood oxygen level-dependent signals across brain regions, also known as functional connectivity (FC) [11]. The default mode network (DMN) is one of the most important and widely studied networks. The DMN plays an active role in complicated cognitive processing, and abnormal alterations of the DMN have been shown in various neuropsychological diseases related to cognitive impairment, such as AD [12] or other types of dementia [13], depression [14], and schizophrenia [15]. The DMN is commonly subdivided into three subcomponents or subsystems, namely, the core subsystem, the medial temporal subsystem, and the dorsal medial subsystem [16]. Each subsystem has several central hubs that are involved in complex cognitive functions [17]. The three subsystems interact as a unit to maintain normal cognition and self-generated experience [18], and the subsystems are usually recruited during unconstrained resting-state periods.

Both disruption in the equilibrium and disassociation of the DMN subcomponents are observed in those with AD, type 2 diabetes mellitus (T2DM), major depression, and the apolipoprotein E (ApoE) type 4 allele [19–23]. However, the changing patterns of the DMN subcomponents and the associations of these changes with cognitive impairment in hypertensive patients are still unclear. There have even been a limited number of studies on the alterations in RSNs in hypertensive patients; only Li et al. [24] found that defective WM and impaired functional connectivity of frontoparietal networks may account for the underlying mechanisms of cognitive impairment in hypertensive patients. Therefore, it is necessary to explore the impaired characteristics of the DMN in hypertensive patients.

In the present study, hypertensive patients with normal cognition (HTN-NC), hypertensive patients with cognitive impairment (HTN-CI) and healthy controls underwent multimodal MRI scans and neuropsychological tests. DMN patterns were identified in each group. The present study aimed to explore the FC alterations in the DMN of hypertensive patients with and those without cognitive impairment and to determine probable imaging markers for the prediction of cognitive impairment in hypertensive patients. We hypothesized that a trend of disassociation of the DMN subsystems would be observed in hypertensive patients and that altered DMN patterns would be disparate between hypertensive patients with and without cognitive impairment.

Methods and materials

Participants

This study was approved by the Nanjing Drum Tower Hospital Ethics Committee in January 2017. The subjects of this research were recruited from among the outpatients and inpatients in our department of neurology. All the participants gave written informed consent prior to participation. All subjects underwent neuropsychological tests, MRI scanning, and computed tomography angiography (CTA) or B-mode ultrasonography of the intracranial and carotid arteries.

All the patients in the hypertensive group were over 50 years old, were diagnosed by the same experienced physician and had a history of taking oral antihypertensive drugs based on their medical records. Based on the standards described in the guidelines [25], each hypertensive patient was classified into different hypertension levels at the same time. The control group included cognitively normal people (age >50 years) without any history of high blood pressure. The exclusion criteria of this research were as follows: (1) dementia (e.g., AD, stroke-related dementia, and other types of dementia), depression and other mental disorders; (2) a long history of taking hypnotic sedative drugs and psychotropic drugs; (3) acute or subacute ischemic stroke and cerebral hemorrhage or a history of stroke (with a diameter of infarction larger than 15 mm on MRI); (4) a history of alcohol dependence, Parkinson's disease, epilepsy, and thyroid gland disease; (5) more than 5 cerebral microbleeds (CMBs) or severe WM lesions (reaching the degree of Fazekas III according to the Fazekas scale [26]); (6) contraindications of MRI scanning or poor quality of the images; and (7) severe intracranial artery or carotid artery stenosis (larger than 50% stenosis or occlusion of the responsible artery). To guarantee the congruity of the images, all the images in this study were collected via the same MRI machine.

Neuropsychological evaluation

A professional neuropsychologist performed the neuropsychological tests before or on the day of the MRI scanning. Physical examinations were also conducted to determine positive neurological signs. The Chinese translation of the Mini-Mental State Examination (MMSE) and the Montreal Cognitive Assessment (MoCA) served as the general cognitive tests. Subjects with cognitive impairment were distinguished from subjects with normal cognition by the MMSE and MoCA scores and their educational experience. The cut-offs of cognitive impairment for the MMSE were made based on the results of the Beijing study (Table 1) [27]. Due to the low specificity of identifying

Table 1 The evaluation criteria of general cognitive function

Cognitive test	Education (years)	Borderlines of cognitive impairment (scores)
MMSE	0	≤19
	1–6	≤22
	>6	≤26
MoCA	0	≤13
	1–6	≤19
	7–12	≤24
	>12	≤25

The subjects with different educational experience who got scores equal to or lower than the borderlines in MMSE or MoCA tests were defined as cognitive impairment.

MMSE Mini-Mental State Examination, MoCA Montreal Cognitive Assessment

cognitively normal people by using 25/26 as a cut-off for individuals with 12 years or less of education, the normative data for the MoCA were formulated according to several studies in the population in China (Table 1) [28, 29]. The subjects with scores lower than or equal to the cut-off points of MMSE or MoCA were defined as cognitive impairment (Table 1). According to the status of general cognitive function, the hypertensive patients were divided into an HTN-NC group ($n = 30$) and an HTN-CI group ($n = 25$). Furthermore, 19 healthy subjects with normal cognition served as a control group.

Memory was assessed using the visual reproduction (VR)–long-delayed recall portion of the Wechsler Memory Scale (WMS) and the Auditory Verbal Learning Test (AVLT) delayed recall test. Language was assessed using the category verbal fluency (VBF) test and the Boston Naming Test (BNT). Processing speed was assessed using the Trail Making Test A (TMT-A) and the Stroop-B test. Executive function was evaluated using the Trail Making Test B and the Stroop-C test. Visuospatial ability and attention were evaluated using the visual reproduction–copy (VR-copy) portion of the Wechsler Memory Scale and the Clock Drawing Test (CDT).

MRI data acquisition

All subjects were scanned using a Philips Ingenia 3.0-T scanner (Philips, Eindhoven, Netherlands) with a 32-channel head coil. See Supplementary Information for details.

Image preprocessing

The imaging data were analyzed using the toolbox for Data Processing & Analysis for Brain Imaging (DPABI) V2.3 (<http://rfmri.org/dpabi>). See Supplementary Information for details.

White matter hyperintensity segmentation and quantification

For the analysis of the WM, gray matter (GM), and CSF volumes, three-dimension fast field echo (3D FFE) images were segmented using SPM8 (statistical parametric mapping, <http://www.fil.ion.ucl.ac.uk/spm>) and the VBM8 toolbox. The Wisconsin White Matter Hyperintensities Segmentation Toolbox (W2MHS) [30] was used to extract and analyze the total white matter hyperintensity (WMH), periventricular WMH, and deep WMH volumes. Taking into account individual cerebral differences, the adjusted WMH was computed with the proportion of the total WMH accounting for the sum of the WM and GM.

Definition of the DMN

A 5-mm-radius sphere in the posterior cingulate cortex (PCC) hub [Montreal Neurological Institute (MNI) space: $-2, -45, 34$] served as a seed region. The mean time series of the seed region was calculated as the reference time course for each participant. The correlation coefficient of each voxel was computed by a Pearson cross-correlational analysis between the seed time course and the time course of each voxel in the whole brain. To obtain the eventual individual maps of the DMN, Fisher's z -transformation was applied in the calculation of the approximately normally distributed correlation coefficients by the equation: $z = 0.5 \times \ln \frac{1+r}{1-r}$. Last, the individual maps of each network were acquired. The one sample t -test was used to identify the brain regions that positively correlated with each seed. The thresholds were set at a corrected $P < 0.001$, determined by Monte Carlo simulations for multiple comparisons (voxelwise $P < 0.001$, FWHM = 6 mm, cluster size $> 486 \text{ mm}^3$).

Statistical analysis

Demographic, clinical, and neuropsychological data

SPSS 23.0 (statistical program for social sciences, SPSS Inc. Chicago, IL) was used to perform all the statistical procedures. Comparisons of age, gender, and some demographic and neuropsychological data were performed by one-way analysis of variance (ANOVA) or the X^2 test. Some categorical data, such as hypertension level and the existence of lacunar infarctions (LIs) and CMBs, were also compared by the chi-square test. The Kruskal–Wallis test was applied in the comparisons of nonnormally distributed demographic and neuropsychological data. Multiple linear regression was also used, controlling for gender, years of education, and age of all subjects. The results are presented in Supplementary Table 1. The threshold for statistical significance was set at $P < 0.05$.

FC analysis

All the functional MRI data were analyzed by REST (<http://restingfmri.sourceforge.net>) and DPABI V2.3. To analyze the DMN FC differences among the 3 groups, an ANCOVA was performed on the individual normalized maps in a voxelwise manner within a GM mask. Age, gender, years of education, head motion parameters, and the modulated GM maps obtained from the T1 segmentation were included as covariates in all the functional data analyses. The threshold was set at a corrected $P < 0.05$, as determined by Monte Carlo simulations (AlphaSim program in AFNI, <http://afni.nih.gov/afni/docpdf/AlphaSim.pdf>), for multiple comparisons in the whole brain (voxelwise $P < 0.01$, FWHM = 6 mm, cluster size $>999 \text{ mm}^3$).

The average FC strength of each significant region of interest (ROI) was extracted from each subgroup by REST 1.7 and was analyzed by SPSS 23.0 afterwards. Post hoc tests (significance was set at <0.05) were performed to explore the differences in FC among the subgroups. Spearman correlational analyses were performed in a ROIwise manner to explore the associations between the DMN FC values and cognitive performance and WMH volume in the hypertensive patients.

Results

Demographic and neuropsychological characteristics

No significant differences in gender, education, WMH volumes, hypertension duration, hypertension level, the number of LIs, the number of CMBs, or the number of subjects with T2DM (Table 2) were shown among the three groups. However, the individuals in the control group were significantly younger than those in hypertensive groups ($P < 0.001$, Table 2). The results of multiple linear regression analysis controlling for age, gender, and education (Supplementary Table 1) were in accordance with the results in Table 2. Significant differences in the MoCA, Stroop-B, and VR-delayed recall scores were shown among the three groups (Table 2, Supplementary Table 1). Specifically, the patients in the HTN-CI group had significantly lower scores on the MoCA than those in the other two groups ($P < 0.001$).

DMN activity in hypertensive patients

A typical spatial pattern of the DMN similar to that observed in a previous study with healthy normal subjects [31] was presented in all groups and included the anterior cingulate cortex, medial prefrontal cortex, lateral prefrontal cortex, precuneus, PCC, and medial temporal lobe (Fig. 1).

The comparison among the control, HTN-NC and HTN-CI groups showed that the ROIs with significant differences were mainly found in the frontal cortex, parietal cortex, and cingulate cortex (Table 3 and Fig. 2). Importantly, based on the division of the brain regions and their associated DMN subsystems in previous studies [16, 32], these regions mainly belonged to the core subsystem and the dorsal medial subsystem (Table 3). Since the hypertensive subjects were significantly older than control subjects, the effect of age on the ROIs with significant differences was investigated with and without age as a covariate, and the results were approximately similar (see Supplementary Fig. 1).

Post hoc analysis: As shown in Fig. 3a, b, compared with the control group, the HTN-NC group displayed a trend of dissociation among the DMN subsystems, i.e., decreased FC in the dorsal medial subsystem (including the left middle temporal gyrus, bilateral precentral gyrus, and medial frontal gyrus) (Fig. 3a) and increased FC in the core subsystem (including the right superior frontal gyrus, right supramarginal gyrus, bilateral angular gyrus, and dorsal anterior cingulate cortex) (Fig. 3b). In contrast, the HTN-CI group displayed significantly increased FC in all regions, with group differences compared to the control group. Notably, although most of the FC intensity differences between the HTN-NC group and the control group were not significant, a tendency of disassociation among the DMN subsystems was evident in the HTN-NC group.

Brain-behavior association analysis in hypertensive patients with cognitive impairment

No significant correlations between the WMH volumes and the DMN FC values were observed in the HTN-CI group (Supplementary Table 2). The FC strength of the dorsal medial subsystem was significantly correlated with the cognitive performance of the HTN-CI patients (Fig. 4). Specifically, the FC values in left middle temporal gyrus were negatively correlated with the MMSE scores in the HTN-CI group ($\rho = -0.438$, $P = 0.029$). Significant negative correlations were also observed between the MoCA scores and the FC values in the left medial frontal gyrus ($\rho = -0.449$, $P = 0.025$), the BNT scores and FC values in the right precentral gyrus ($\rho = -0.419$, $P = 0.037$), and the BNT scores and the FC values in the right medial frontal gyrus ($\rho = -0.415$, $P = 0.039$).

Discussion

The present study found a tendency of disassociation among the DMN subsystems in HTN-NC patients and extensively increased connectivities among the DMN subsystems in

Table 2 Demographic, clinical and neuropsychological data

	Control (<i>n</i> = 19)	HTN-NC (<i>n</i> = 30)	HTN-CI (<i>n</i> = 25)	<i>P</i> value/ χ^2
Age, years	57.26 ± 7.08	65.93 ± 7.83 ^a	65.32 ± 7.63 ^a	<0.001 ^{***}
Gender (male/female)	10/9	16/14	12/13	0.918
Education, years	12 (6.00)	12 (6.50)	12 (5.50)	0.424
Diabetes mellitus, <i>n</i> (%)	5 (26.32)	8 (26.67)	7 (28.00)	0.991
HTN duration, years	—	10 (9.13)	6 (7.50)	0.295
<i>HTN level</i>	HTN-1, <i>n</i> (%)	10 (33.30)	8 (32.00)	0.719
	HTN-2, <i>n</i> (%)	10 (33.30)	11 (44.00)	
	HTN-3, <i>n</i> (%)	10 (33.30)	6 (24.00)	
<i>WMH degree</i>	Fazakes I, <i>n</i> (%)	16 (84.20)	22 (88.00)	0.724
	Fazakes II, <i>n</i> (%)	3 (15.80)	3 (12.00)	
Lacunar infarction, <i>n</i> (%)	1 (5.26)	5 (16.67)	6 (24.00)	0.247
Cerebral microbleed, <i>n</i> (%)	1 (5.30)	7 (23.30)	5 (20.00)	0.247
Gray matter volume, cm ³	545.54 ± 31.00	527.32 ± 42.92	536.98 ± 54.42	0.240
White matter volume, cm ³	486.61 ± 40.19	454.47 ± 43.91	472.99 ± 54.98	0.065
TWMH volume, mm ³	547.23 (498.72)	1002.30 (1795.42)	956.41 (2316.82)	0.115
PVWMH volume, mm ³	204.32 (463.06)	582.20 (1396.06)	786.85 (1396.5)	0.154
DWMH volume, mm ³	76.22 (281.44)	138.97 (439.04)	189.62 (507.58)	0.378
WMH adjusted	5.41 × 10 ⁻⁴ (4.59 × 10 ⁻⁴)	10.14 × 10 ⁻⁴ (18.10 × 10 ⁻⁴)	5.41 × 10 ⁻⁴ (4.59 × 10 ⁻⁴)	0.122
MMSE	29 (2.00)	28.5 (2.00)	29 (2.00)	0.365
MoCA	27 (1.00)	26 (2.00)	23 (5.00) ^{a,b}	<0.001 ^{***}
HAMD	4 (9.00)	3 (8.00)	3 (7.00)	0.900
<i>Processing speed</i>				
TMT-A(s)	47 (29.00)	52 (15.75)	47 (26.00)	0.159
Stroop-B(s)	17 (9.00)	19 (5.25)	23 (6.00) ^b	0.023 [*]
<i>Executive function</i>				
TMTba(s)	37 (36.00)	31.5 (45.50)	51 (50.00)	0.193
Stroop CB(s)	6 (10.00)	10.5 (15.25)	10 (10.00)	0.416
<i>Working memory</i>				
AVLT-long term delay recall	5.79 ± 2.37	4.96 ± 2.01	4.80 ± 2.93	0.796
(WMS)VR- delay recall	9.10 ± 2.88	6.68 ± 3.32	6.36 ± 4.37 ^a	0.033 [*]
<i>Language</i>				
Boston naming test	52 (5.00)	53 (6.75)	49 (14.50)	0.549
Category verbal fluency	16.95 ± 3.84	17.39 ± 3.66	16.20 ± 2.87	0.35
<i>Visual-spatial ability</i>				
(WMS)VR-copy	14 (0.00)	14 (0.00)	14 (0.00)	0.581
CDT	4 (0.00)	4 (0.00)	4 (1.00)	0.061

HTN-NC hypertensive patients with normal cognition, *HTN-CI* hypertensive patients with cognitive impairment, *HTN* hypertension, *WMH* white matter hyperintensities, *PVWMH* periventricular white matter hyperintensities, *DWMH* deep white matter hyperintensities, *MMSE* Mini-mental State Examination, *MoCA* Montreal Cognitive Assessment, *HAMD* Hamilton Depression Scale, *TMT* Trail Making Test, *AVLT* Auditory Verbal Learning Test, *WMS* Wechsler Memory Scale, *VR* Visual Reproduction, *CDT* clock drawing test.

Data are represented as mean ± SD, *n* (%) or median (IQR), ^a*P* < 0.05, differs from the control group; ^b*P* < 0.05, differs from the HTN-NC group, ^{*}*P* < 0.05, ^{***}*P* < 0.001. One-way ANOVA was applied in the comparison of normal distributed data, χ^2 test was applied in the ranked data. The Kruskal–Wallis test was used for the comparisons of non-normal distributed data

HTN-CI patients. The increased connectivities in the dorsal medial subsystem were associated with poor cognitive performance in the HTN-CI patients. These findings could contribute to the understanding of the mechanisms underlying cognitive impairment in hypertension and could provide potential imaging biomarkers for cognitive impairment related to hypertension.

Although there were no significant differences between the FC of the HTN-NC group and of the control group, there still existed a disassociation trend among the DMN

subsystems, i.e., decreased FC in the dorsal medial subsystem and increased FC in the core subsystem. The disruption of the equilibrium among the DMN subcomponents has also been observed in other diseases, such as AD [19], major depression [20], and particularly T2DM [22]. The DMN subsystems act as a whole and interact in a dynamic equilibrium that is critical for the maintenance of normal cognition [33]. The small-world properties are remarkably impaired in AD patients [34], indicating disruption of brain networks and the inability to integrate brain networks. The

Fig. 1 The DMN were constructed in the control group, HTN-NC group, HTN-CI group separately by the one sample *t*-test. The thresholds were set at a corrected $P < 0.001$, determined by Monte Carlo simulation for multiple comparisons. DMN default mode network, HTN-NC hypertensive patients with normal cognition, HTN-CI hypertensive patients with cognitive impairment

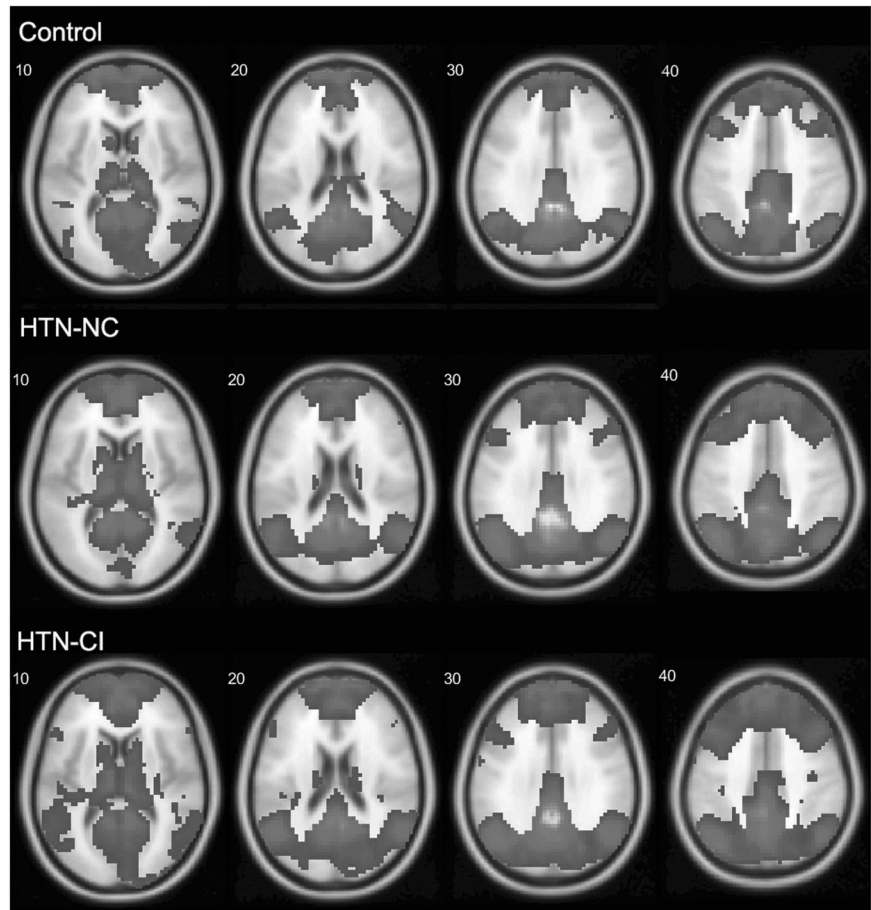


Table 3 Brain regions with significant differences in DMN functional connectivity between groups

Regions	BA	Volume (mm ³)	Peak MNI coordinate (mm)			Maximal <i>F</i> -value
			(x, y, z)			
<i>Dorsal medial subsystem</i>						
L Middle Temporal Gyrus	21	999	-57	0	-18	7.953
L Middle Temporal Gyrus	22	2403	-57	-39	3	8.740
R Precentral Gyrus	4	3051	42	-18	57	9.221
L Precentral Gyrus	6	1458	-30	-3	63	7.230
R Medial Frontal Gyrus/ R Superior Frontal Gyrus	6	3402	18	-3	66	9.516
L Medial Frontal Gyrus	6	2376	-6	-12	60	6.829
<i>Core subsystem</i>						
R Superior Frontal Gyrus	10	1296	21	57	12	9.030
R Angular Gyrus	39	1647	45	-69	30	8.580
R Supramarginal Gyrus	22	1242	63	-48	21	8.497
L Angular Gyrus	39	1323	-45	-66	30	6.832
Cingulate Gyrus	32	3645	6	18	42	7.862

(x, y, z) coordinates of primary peak locations in the MNI space.

DMN default mode network, *L* left, *R* right, *BA* Brodmann area, *MNI* Montreal Neurological Institute

Fig. 2 The DMN FC differences among the three groups. According to the ANCOVA, the 11 brain regions with significant differences were mainly located in the frontal cortex, parietal cortex, and cingulate cortex. The thresholds were set at a corrected $P < 0.05$, determined by Monte Carlo simulation for multiple comparisons (voxelwise $P < 0.01$, FWHM = 6 mm, cluster size $> 999 \text{ mm}^3$). L left, R right, DMN default mode network, FC functional connectivity, ANCOVA analysis of covariance

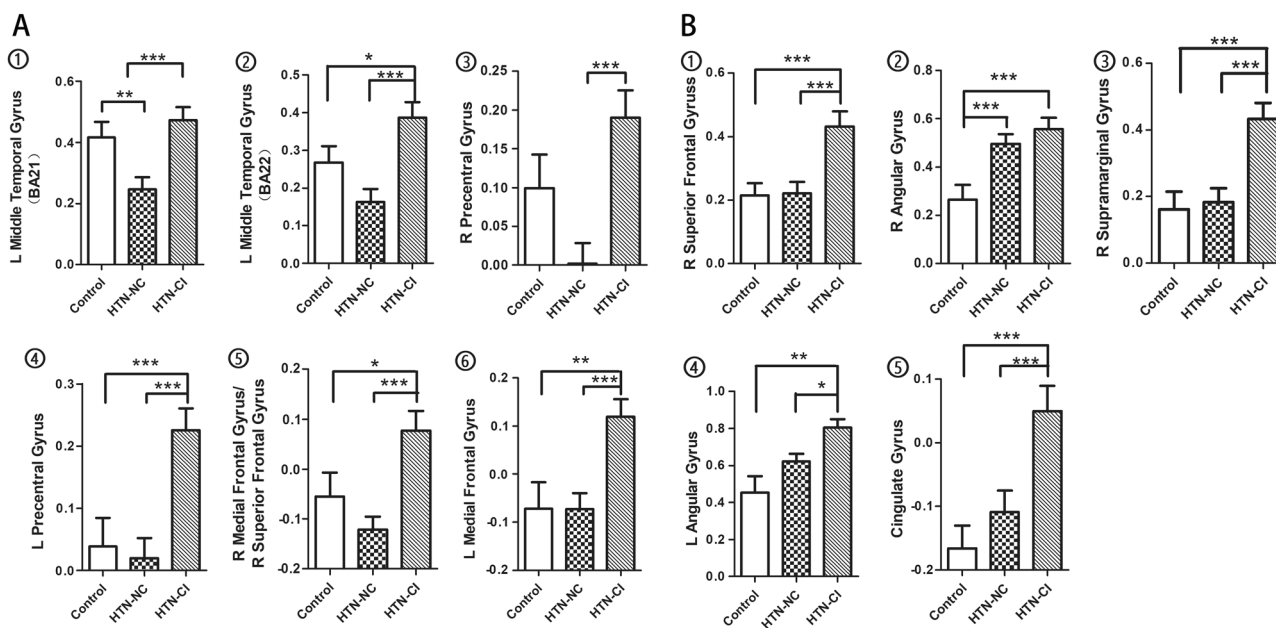
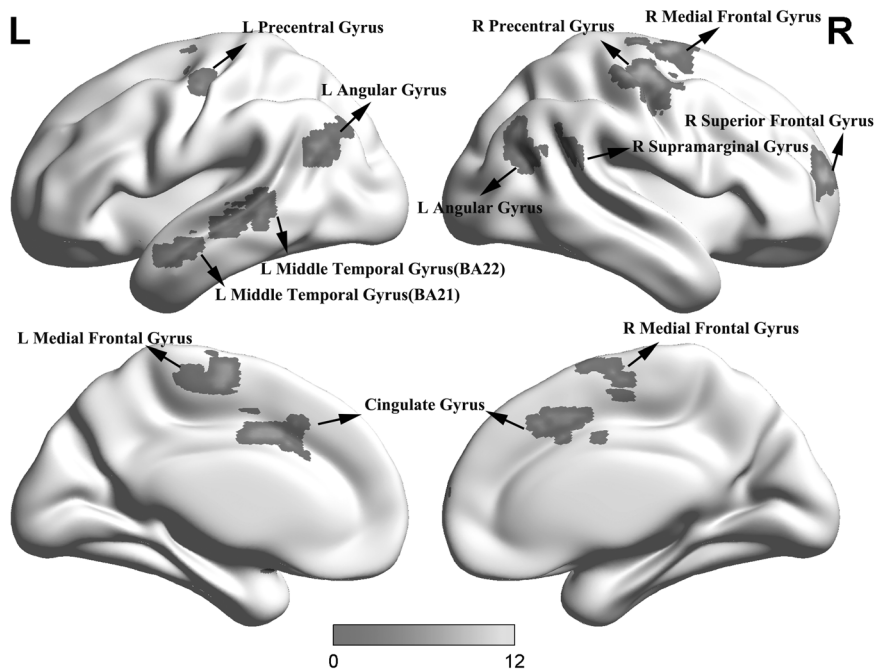


Fig. 3 DMN FC differences among the three groups in (a) the dorsal medial subsystem and (b) the core subsystem. A tendency of dissociation among the DMN subsystems was found in the HTN-NC group, while an overall significant FC enhancement appeared in all the brain regions in the HTN-CI group. The significant differences

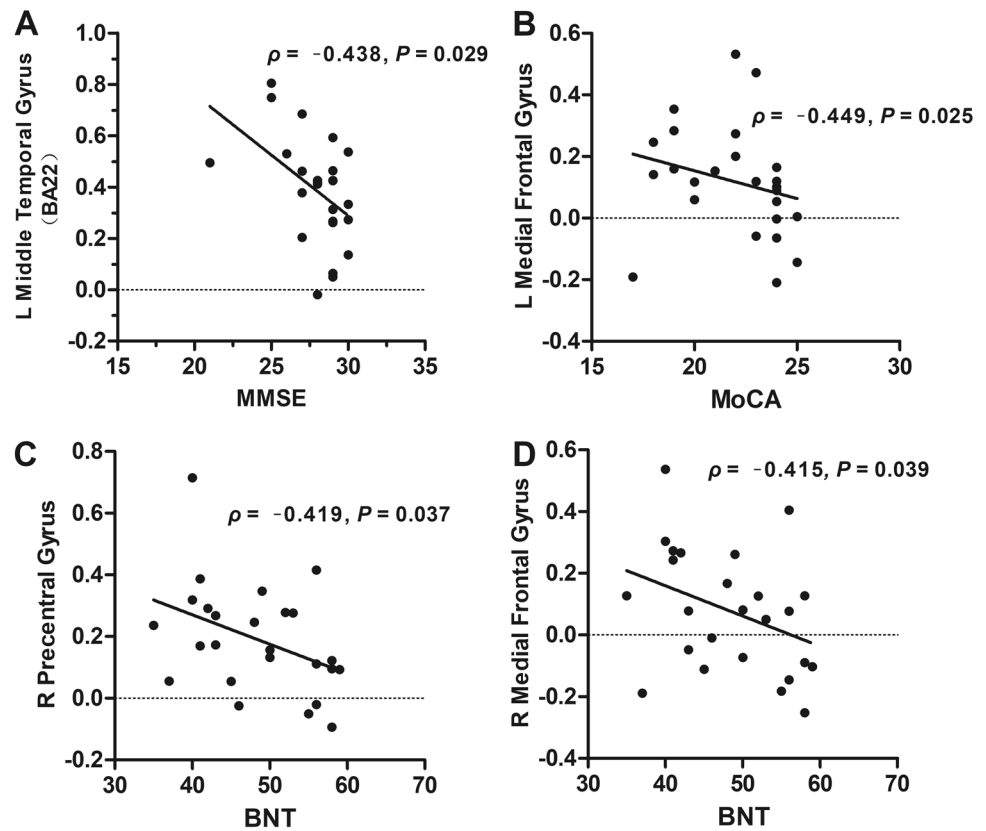
between each pair of groups in different brain regions according to the post hoc analysis are marked (* $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$). L left, R right, DMN default mode network, FC functional connectivity, HTN-NC hypertensive patients with normal cognition, HTN-CI hypertensive patients with cognitive impairment

present study is the first to show a tendency of dissociation among the DMN subsystems in hypertensive patients, suggesting that the internal balance and integrity of the DMN subsystems is disrupted by hypertension. However, the tendency of dissociation within the DMN was found only in hypertensive patients with normal cognition. Thus,

it is possible that merely the trend of dissociation among the DMN subsystems would not confer to cognitive impairment in hypertensive patients.

HTN-CI patients showed significant FC increases in both the dorsal medial subsystem and core subsystem of DMN, and previous studies have revealed a similar compensatory

Fig. 4 Spearman correlation analysis was performed to detect the relationship between DMN FC and cognitive performance in the HTN-CI group. Increased functional brain activity was associated with worse cognitive performance. **a** The FC of the L middle temporal gyrus (BA22) had a negative correlation with MMSE score. **b** The FC of the L medial frontal gyrus was negatively correlated with MoCA score. **c, d** The FCs of the R precentral gyrus and the L medial frontal gyrus showed inverse correlations with BNT score. L left, R right, BA Brodmann area, DMN default mode network, FC functional connectivity, HTN-CI hypertensive patients with cognitive impairment, MMSE Mini-Mental State Examination, MoCA Montreal Cognitive Assessment, BNT Boston Naming Test



phenomenon in MCI, AD [35–37], Parkinson’s disease [38], and schizophrenia [39]. This compensation can be seen as a process of brain reconstruction and brain functional remodeling due to its plasticity after damage to original neural networks, especially in the early phase of CI [36, 40]. It should be noted that the abnormally increased FC appeared in the preliminary stage, presented a declining trend with progression of the disease and vanished at the terminal stage of the disease [41]. To compensate for the cerebral damage concomitant with the cognitive decline, the impaired region of brain could reallocate the cognitive and neurological resources from the whole brain [35]. Therefore, the HTN-CI patients may have the chance to inhibit the aggravation and prevent cognitive impairment since they are still in the initial stage of CI. Recent neuroimaging studies have confirmed that DMN changes could predict therapeutic effects in psychiatric disorders such as schizophrenia [42]. Similarly, the compensatory phenomenon of the DMN in HTN-CI patients may also hold great potential value for providing information about early prediction of cognitive impairment prognosis and treatment in hypertensive patients.

Interestingly, the changing patterns in the dorsal medial subsystem were prominently different between the HTN-NC patients and the HTN-CI patients, indicating that the function of the dorsal medial subsystem plays a

predominant role in the cognitive impairment of these hypertensive patients. Our investigations further found significant negative relationships between the dorsal medial subsystem and corresponding neuropsychological tests of overall cognitive function and language ability, such as the MMSE, MoCA, and BNT, in HTN-CI patients. These findings were in line with those of previous studies that found that the dorsal medial subsystem mainly participates in semantic processing and comprehension of conceptual knowledge components [17]. Thus, we postulated that the increased FC in the dorsal medial subsystem and its inverse correlations between the neuropsychological results is more closely related to the cognitive compensation for the damage to brain function and loss of manipulation in HTN-CI patients.

WMH is common in hypertensive patients. The structural basis of brain function is the neuronal connections among various regions via WM tracts [43]. However, the present study found no association between the DMN FC value and WMH grade or WMH volume in hypertensive patients, a finding that did not coincide with the assumption that WMH is the main factor that contributes to the FC alterations related to hypertension. The following are possible reasons. The microstructural integrity of the WM in particular regions could play a key role in specific cognitive disturbances [44]; however, the present volumes of the

WMH presented only as a macroscopic lesion of the white matter tracts. It is clear that the occurrence of cognitive decline is the result of the interaction between brain structure and function, and more detailed and precise studies of the microstructure in WM tracts could lead to more reliable conclusions.

Limitations and future work

Several limitations need to be addressed. First, the sample size was relatively small for making the conclusions persuasive. Since the current study was a cross-sectional study, it is uncertain that the obtained results were causes of hypertension-induced cognitive impairment or the results of hypertension-induced cognitive impairment. Thus, we intend to enlarge the sample size and follow up subjects for three or four years to investigate the association between alterations of cognitive performances and those of brain network activity. The continuous follow-up of blood pressure fluctuations, cognition and DMN alterations of all subjects is underway.

Additionally, the diversity of antihypertensive drugs, hypoglycemic drugs, and lipid-lowering drugs were not analyzed in the present study. An effective blood pressure control can retard the speed of hypertension progression, and different drugs generate different therapeutic effects. No studies have specifically explored the effects of hypoglycemic drugs or lipid-lowering drugs on brain networks. Even the effects of those drugs on cognition are controversial. Both beneficial effects (cognitive protection [45] and reducing the risk of AD [46]) and neurotoxic effects (aggravating the cognitive impairment [47, 48]) were found in previous studies. The LIs and T2DM may have affected the present findings, although these confounding factors were comparable among the three groups. As it is difficult to control the effects of different drugs and other diseases, exclusion of those patients with LIs, T2DM, and hyperlipidemia in a future study would be a wise choice to alleviate the effects of different confounding factors.

Last but not least, the diagnosis of hypertension was based on medical records and history of taking oral antihypertensive drugs. The assessment of previous BP control is difficult in patients with long-term hypertension. Thus, home BP monitoring (HBPM) plays an important role in hypertension management and evaluation of BP control [25]. HBPM is more closely related to hypertension-induced organ damage than is clinical BP measurement [25], and the variability of home BP has been associated with cognitive decline in hypertensive patients [49, 50]. Since the variability could also be an important influencing

factor of brain network activity and cognition, we would like to calculate the variability of home BP through the records of HBPM and 24-h ambulatory BP measurement in future follow-up visits.

Conclusion

Different brain network alterations in the core subsystem and the dorsal media subsystem of DMN may differentiate hypertensive patients with cognitive impairment from those with normal cognition. HTN-CI patients displayed extensively increased connectivities in the DMN subsystems that were associated with poor cognitive performance. The characteristic changes in the dorsal medial subsystem may become an early imaging biomarker for cognitive impairment in hypertensive patients.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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