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RESEARCH ARTICLE

Quantitative Susceptibility Mapping of Brain Iron Relating to Cognitive Impairment in Hypertension

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Background: Hypertension (HTN) might impair cognition. Brain iron deposition correlates with cognitive impairment. The relationship between brain iron and cognition in HTN patients is less clear.
Purpose: To measure brain susceptibility in HTN patients using quantitative susceptibility mapping (QSM) and to explore the relationship between brain iron and cognition.
Study Type: Retrospective cross-sectional study.
Subjects: Sixty HTN patients (35 with mild cognitive impairment [MCI] and 25 without MCI) and 24 age, gender, and education matched controls.
Field Strength/Sequence: 3 T; strategically acquired gradient echo (STAGE) imaging protocol for QSM analysis.
Assessment: All subjects underwent Montreal Cognitive Assessment (MoCA) scoring of visuospatial/executive, naming, attention, abstraction, language, delayed memory, and orientation functions. HTN patients were divided into two groups (with and without MCI) depending on the MoCA score. Regions of interest (ROIs) were manually demarcated on the STAGE images by three independent radiologists and susceptibility were determined for bilateral frontal white matter, parietal white matter, occipital white matter, caudate nucleus (CN), putamen (PU), globus pallidus (GP), thalamus (TH), red nucleus (RN), substantia nigra (SN), and dentate nucleus (DN).
Statistical Tests: Analysis of variance with post-hoc least significant difference (LSD) tests and Pearson correlation coefficients (r). A P-value <0.05 was considered to be statistically significant.
Results: The susceptibility was significantly different in CN, PU, and DN among the three groups. The susceptibility of right CN and left PU were correlated with MoCA scores ($r = -0.429$ and $r = -0.389$, respectively). The susceptibility of left PU was also correlated with delayed memory scores ($r = -0.664$). The susceptibility of left and right GP were correlated with naming scores ($r = -0.494$ and $r = -0.446$, respectively) and the susceptibility of left DN were correlated with visuospatial/executive scores ($r = 0.479$).
Data Conclusion: QSM measured brain iron was significantly higher in CN, PU, and DN in HTN patients. Cognitive impairment was correlated with regional brain iron deposition.
Level of Evidence: 2
Technical Efficacy: Stage 3

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Hypertension (HTN) is one of the most common chronic diseases worldwide, affecting an estimated half of all Chinese adults aged 35–75 years.[1] As the leading risk factor for cardiovascular events, HTN induces hypertrophy and degenerative changes of the cerebral vessel wall, which in turn damage the white matter and gray matter of the brain through changes of blood supply and inflammation.[2] There is also substantial evidence that HTN is associated with cognitive decline, with HTN being an independent risk factor for Alzheimer's disease, vascular dementia, and mild cognitive

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impairment (MCI).[2,3] MCI may affect up to 12% of patients with HTN, but the mechanisms of how it occurs are unclear. It is currently believed that changes in cerebrovascular function and structure, alteration of brain blood perfusion, brain atrophy, and vascular amyloid-β accumulation may play an important role.[2] However, the role of iron deposition is unclear.

Iron is one of the most important trace elements found in the human body and the homeostasis of iron is essential for maintaining normal functions of the brain.[4,5] In recent years, several studies have shown that excessive brain iron deposition is related to neurodegeneration and cognitive impairment.[4,6] Cardiovascular risk factors, including HTN, may change the permeability of the blood–brain barrier (BBB) and induce inflammation, leading to abnormal accumulation and distribution of brain iron.[7] In particular, it has been reported that brain iron in the hippocampus, caudate nucleus (CN), putamen (PU), entorhinal cortex, superior frontal gyrus, and primary visual cortex of HTN patients was significantly elevated.[8] Therefore, we speculate that brain iron deposition may also play an important role in the development of cognitive impairment in HTN patients.

Quantitative susceptibility mapping (QSM) is an magnetic resonance imaging (MRI) method that is based on gradient-echo phase images to quantify the spatial distribution of magnetic susceptibility in biological tissues, and can be used to noninvasively measure tissue iron content with high spatial resolution and high sensitivity.[9,10] Currently, the distribution of brain iron deposits in patients with HTN is unclear, as is the relationship between brain iron deposition and cognitive decline in HTN. Thus, the aim of this study was to use QSM to assess brain iron deposition in HTN, and to study the correlation between iron deposition in various brain regions and cognitive function.

Materials and Methods

This study was approved by the Medical Ethics Committee of our hospital and conducted in accordance with the Declaration of Helsinki. All participants signed an informed consent form.

This research is based on a retrospective analysis of data acquired for a previous prospective study.[11] From October 2019 to June 2021, 92 patients diagnosed with primary HTN were recruited in our hospital. The diagnosis of HTN was based on 2010 Chinese guidelines for the management of HTN,[1] defined as systolic blood pressure (SBP) ≥140 mmHg or diastolic blood pressure (DBP) ≥90 mmHg, and/or those who had used antihypertensive medicine within the last 2 weeks. A total of 41 normal controls without a history of nervous system disease, vascular risk factors, cognitive impairment, or psychiatric illness were recruited through advertisements, and were matched with the HTN patients in terms of age, gender, and education. Exclusion criteria included: 1) alcoholism, brain injury, Parkinson's disease, epilepsy, dementia, severe depression, or other neurological disorders; 2) visual and hearing impairments and other serious systemic diseases such as malignant tumors, kidney dysfunction, or autoimmune diseases; 3) severe claustrophobia or MRI contraindications, and 4) failure to complete neuropsychological examination. Participants underwent MRI and all images were evaluated by an experienced interventional radiologist (C.Z., 30 years' experience), two neuroradiologists (L.W., 15 years' experience and W.W., 5 years' experience) all of whom were blinded to the subjects' clinical and cognitive data. Participants with severe white matter disease, infarction (except lacunar infarction), or cerebral hemorrhage (except cerebral) microbleeds were excluded from further analysis.

After screening the subjects according to the results of image evaluation, 60 HTN patients (24 women and 36 men), with an average age of 61 years (range 42–81 years), an average education level of 9 years (range 0–16 years), an average SBP of 139 mmHg (range 100–179 mmHg), and an average DBP of 83 mmHg (range 65–105 mmHg) were included. All of them self-reported under regular medication. A total of 24 normal controls (13 women and 11 men), with an average age of 59 years (range 44–74 years) and an average education level of 9 years (range 0–16 years) were included. The patients were subdivided into two groups: HTN without MCI (N = 25) and HTN with MCI (N = 35). All diagnoses of MCI were determined according to the criteria proposed by Peterson, and included: memory problems with Montreal Cognitive Assessment (MoCA) score <26 (if years of education ≤12, one point was added to the patient's score), cognitive decline in accordance with age and education, normal function in daily life, and absence of dementia.[12,13]

Montreal Cognitive Assessment

The Chinese Beijing version of the MoCA scale, a cognitive screening instrument created and validated to detect MCI, was administered as our primary outcome measure.[14] This instrument consists of 30 questions that takes approximately 10–12 minutes to complete. It evaluates seven aspects of cognitive sub-domains including: visuospatial/executive function, naming, attention, abstraction, language, delayed memory, and orientation, with a total score of 0–30 (the higher the score, the better the function). A score ranging from 18 to 25, is considered to be an indicator of MCI.[15] To counterbalance the effect of lower education, 1 point was added to the final score of those individuals with <12 years of education.[14,15]

MRI Data Acquisition

All subjects were imaged on a MAGNETOM Skyra 3.0 T MR scanner (Siemens Healthcare, Erlangen, Germany) using a product 32-channel head coil for signal reception. The acquisition parameters followed the strategically acquired gradient echo (STAGE) imaging protocol. This included two double-echo gradient echo (GRE) scans employing a pair of optimal flip angles:[9] 1) Axial double echo (DE) proton density weighted (PDW): repetition time (TR)/echo time (TE) = 7.5/17.5 msec, field-of-view (FOV) =256 mm × 256 mm, flip angle (FA) = 6°, matrix = 384 × 144, slice thickness (TH) = 2 mm, number of slices = 64, voxel size = 0.67 × 1.33 × 2.0 mm^3; 2) axial DE T1W: TR/TE = 8.75/18.75 msec, FOV = 256 mm × 256 mm, FA = 24°, matrix = 384 × 144, TH = 2 mm, number of slices = 64, voxel size = 0.67 × 1.33 × 2.0 mm^3; total scanned acquisition time of 5 minutes 36 seconds. The fluid-attenuated inversion recovery (FLAIR) sequence was scanned using the following parameters:

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TR/TE = 9000/95 msec, FOV = 240 × 240 mm, matrix = 320 × 192, TH = 4 mm, number of slices = 40, and voxel size = 0.9 × 0.9 × 4 mm^3.

Quantitative Susceptibility Mapping Processing

The reconstruction of QSM images was performed using STAGE processing software (STAGE version 2.1.4) with the following steps: skull removal using brain extraction tool, phase unwrapping, background field removal using sophisticated harmonic artifact reduction for phase data (SHARP) algorithm, and an inverse filter with a *k*-space threshold of 0.1.[9,16,17]

Measuring Susceptibility

Three independent radiologists (W.W., 5 years' experience; H.Z., 4 years' experience; Z.Q., 3 years' experience) drew regions of interest (ROIs) on the STAGE maps and measured susceptibility values using SPIN software (SpinTech MRI, Bingham Farms, MI, USA). The ROIs were: bilateral frontal white matter (FWM), parietal white matter (PWM), occipital white matter (OWM), CN, PU, globus pallidus (GP), thalamus (TH), red nucleus (RN), substantia nigra (SN), and dentate nucleus (DN). The ROI in FWM, PWM, and OWM were circular (100 pixels). The susceptibility values of all ROIs measured by each radiologist were recorded for later analysis of the intra-class correlation coefficient (ICC). The final susceptibility value for each ROI was the average of the three radiologists' measurements. The deep gray matter nucleus and white matter were selected as target regions because they contain structures closely related to cognitive, emotional, and motor functions[18] (Figure 1).

Statistical Analysis

Statistical analyses were performed using SPSS software (version 25.0; SPSS, Inc., Chicago, IL, USA), and results were expressed as mean ± SD. The data distribution was tested for normality using the Kolmogorov–Smirnov test. To evaluate the inter-observer reliability of the susceptibility values measurement by three radiologists, the ICC was calculated. Associations between susceptibility values and postmortem brain iron concentrations were explored using Spearman correlation coefficients. Comparisons of the demographic data, clinical data, cognitive scores, and susceptibility values among the three groups were performed using analyses of variance (ANOVAs) for normally distributed continuous data, and the LSD test was used for the post hoc analysis. The Kruskal–Wallis H test was used for non-normally distributed or unequal variances data, and the Mann–Whitney U test was used for the post hoc analysis, with the significance level (α) adjusted by the Bonferroni correction. A χ^2 test was used to compare proportions, and an independent two-sample t test was used to assess the HTN duration, SBP, and DBP. Partial correlation was used to analyze the relationships between the susceptibility values and the MoCA total score and the seven MoCA cognitive sub-domains scores, in the HTN with MCI group, with age and education level as covariates. A P-value less than 0.05 was considered to be statistically significant.

Results

There were no significant differences in age ($P = 0.626$), gender ($P = 0.415$), education level ($P = 0.971$), body mass index ($P = 0.124$), diabetes ($P = 0.890$), and abstraction score ($P = 0.065$) among the three groups. There was no significant difference in the duration of HTN ($P = 0.893$), SBP ($P = 0.393$), and DBP ($P = 0.879$) between the HTN with MCI and the HTN without MCI groups. Compared with normal controls and HTN without MCI, HTN with MCI had a significantly lower MoCA total score, visuospatial/

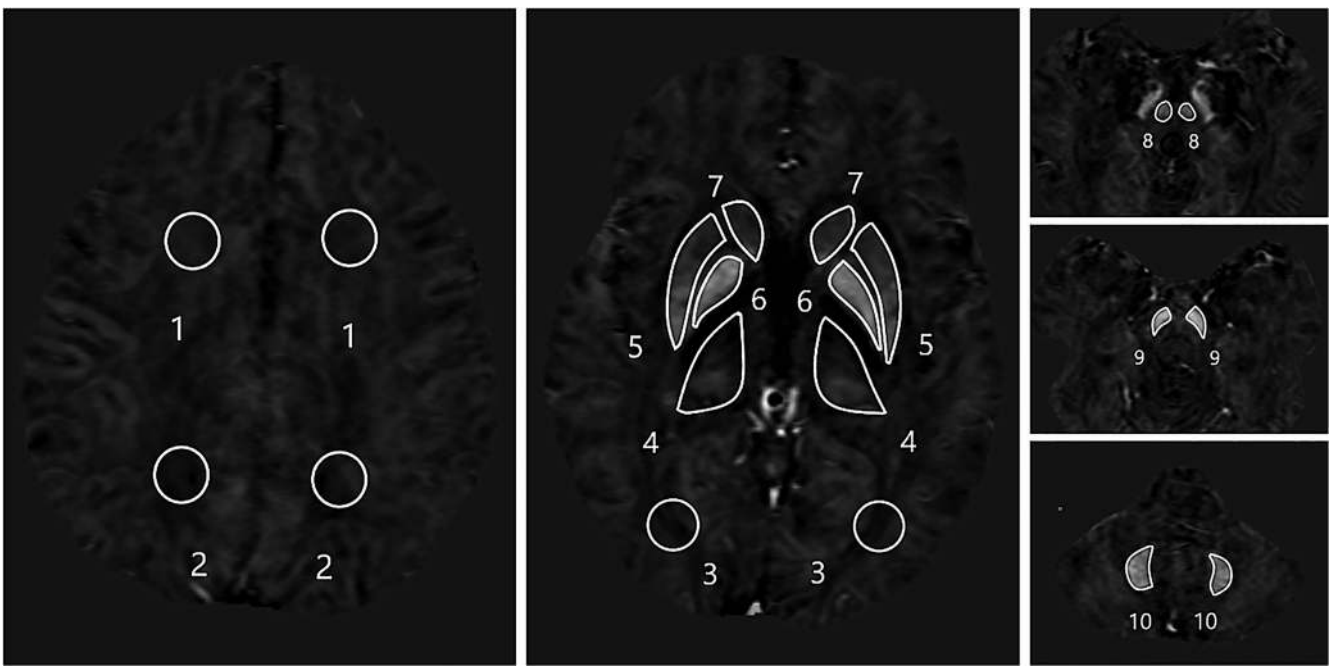

FIGURE 1: Regions of interest (ROI) drew on the quantitative susceptibility mapping (QSM) images. 1 = frontal white matter (FWM); 2 = parietal white matter (PWM); 3 = occipital white matter (OWM); 4 = thalamus (TH); 5 = putamen (PU); 6 = globus pallidus (GP); 7 = caudate nucleus (CN); 8 = red nucleus (RN); 9 = substantia nigra (SN); and 10 = dentate nucleus (DN)

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executive function score, naming score, attention score, language score, delayed memory score, and orientation score (Table 1).

The ICCs of regional susceptibility values between three radiologists were all >0.81 (CN, right ICC = 0.88, left ICC = 0.96; GP, right ICC = 0.94, left ICC = 0.89; PU, right ICC = 0.87, left ICC = 0.91; TH, right ICC = 0.82, left ICC = 0.86; RN, right ICC = 0.91, left ICC = 0.93; SN, right ICC = 0.92, left ICC = 0.90; DN, right ICC = 0.86, left ICC = 0.89; FWM, right ICC = 0.90, left ICC = 0.84; PWM, right ICC = 0.87, left ICC = 0.86; OWM, right ICC = 0.82, left ICC = 0.85).

In the 24 normal controls, the mean susceptibility values of FWM, CN, PU, GP, TH, RN, and SN were −10, 40, 50, 139, −3, 134, and 146 ppb, respectively. The postmortem brain iron concentrations in the corresponding regions reported by Hallgren and Sourander were 4.24, 9.28, 13.32, 21.30, 4.76, 19.48, and 18.64 mg per 100 g of wet weight, respectively. There is a close positive correlation between the susceptibility values obtained in this current study and the iron concentration in the brain reported above ($r = 0.893$; Figure 2).

The susceptibility values of the bilateral CN, PU, and DN of the three groups were significantly different. Compared with normal controls, HTN with MCI had significantly increased susceptibility values in the bilateral CN, PU, and DN. In addition, we found that the HTN without MCI group had significantly increased susceptibility values in the left PU compared with normal controls. The susceptibility values of the bilateral CN of the HTN with MCI group were significantly higher than those of HTN without MCI group (Table 2; Figure 3).

The MoCA total score was significantly correlated with the susceptibility values of the right CN ($r = -0.429$) and the left PU ($r = -0.389$), and the naming score was significantly correlated with the susceptibility values of the left and

TABLE 1. Demographic, Clinical Data, and Cognitive Scores of All Subjects

	HTN With MCI (N = 35)	HTN Without MCI (N = 25)	Normal Controls (N = 24)	*P*-Value
Age (years)	61.23 ± 9.57	61.44 ± 9.88	59.21 ± 7.05	0.626
Gender (male/female)[a]	22/13	15/10	11/13	0.415
Education (years)	9.69 ± 4.16	9.84 ± 3.82	9.58 ± 2.84	0.971
Body mass index (kg/m^2)	24.57 ± 3.04	23.16 ± 2.94	24.59 ± 2.51	0.124
Hypertension duration (years)[b]	8.11 ± 9.43	8.72 ± 7.09	0	0.893
SBP (mmHg)[b]	137.48 ± 20.53	141.63 ± 16.78	/	0.393
DBP (mmHg)[b]	83.52 ± 11.42	83.97 ± 11.15	/	0.879
Diabetes	6	4	3	0.890
MoCA total score[c]	20.06 ± 2.71	26.92 ± 1.15	27.88 ± 1.152	0.001*
Visuospatial-executive score[c]	2.78 ± 1.18	4.13 ± 0.61	4.33 ± 0.76	0.001*
Naming score[c]	2.34 ± 0.78	2.50 ± 0.59	2.88 ± 0.33	0.011*
Attention score	4.06 ± 1.26	5.29 ± 0.90	5.38 ± 0.77	0.001*
Language score	1.13 ± 0.97	2.29 ± 0.80	2.25 ± 0.60	0.001*
Abstraction score	1.13 ± 0.75	1.54 ± 0.58	1.29 ± 0.55	0.065
Delayed recall score[c]	1.22 ± 1.36	3.58 ± 0.97	3.54 ± 0.83	0.001*
Orientation score[c]	5.53 ± 0.76	6 ± 0	6 ± 0	0.001*

[a]The *P*-value was obtained using the χ^2 test.
[b]The *P*-value was obtained using the independent two-sample *t* test.
[c]The *P*-value was obtained using the Kruskal–Wallis *H* test, and the Mann–Whitney *U* test was used for the post hoc analysis, with the significance level (α) adjusted by the Bonferroni correction.
*$P < 0.05$.

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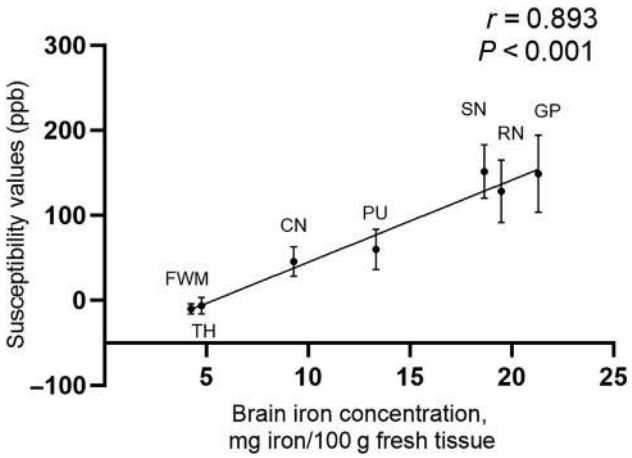

FIGURE 2: Correlation between the brain susceptibility values (ppb) of the normal controls and the real postmortem brain iron concentrations reported by Hallgren and Sourander ($r = 0.893$, $P < 0.001$).

right GP ($r = -0.494$, and $r = -0.446$, respectively). The delayed memory score was significantly correlated with the susceptibility values of the left PU ($r = -0.664$), and the visuospatial/executive function scores was significantly correlated with the susceptibility values of the left DN ($r = 0.479$) (Figure 4a–f).

Discussion

Iron is involved in many fundamental biological processes in the brain including oxygen transportation, DNA synthesis, myelin synthesis, and neurotransmitter synthesis and metabolism.[4,19] Many factors and diseases, such as age, diabetes, depressive symptoms, and neurodegenerative diseases, are related to the content and distribution of brain iron through different mechanisms.[18,20,21] In this study, QSM was used to study the characteristics of brain iron deposition in HTN patients. Our results show that the iron content in the bilateral CN, PU, and DN of the HTN patients with MCI is significantly higher than that of the normal controls, and the iron content of the bilateral CN was significantly higher than that of the HTN patients without MCI. Our results also show that increased susceptibility in the CN, PU, and GP of HTN patients with MCI are negatively correlated with naming scores, delayed memory scores, and MoCA total scores.

Our results are similar to some previous studies. Li et al reported that HTN participants had significantly greater iron content in the CN, PU, GP, and TH.[22] Furthermore, a recent experimental study showed significantly increased total brain iron content in a rat model with HTN using ferrous chromite colorimetry.[23] Based on the results of these clinical and experimental studies, several potential reasons for the increased brain iron content caused by HTN have been suggested: 1) HTN destroys the integrity of BBB which regulates the iron content in the brain and participates in the brain iron transport process;[24] 2) HTN causes arteriosclerosis and abnormal cerebral blood perfusion, resulting in insufficient blood perfusion of the brain's microstructure, and short-term ischemia of the striatum may cause abnormal iron deposition;[25] and 3) HTN causes cerebral vascular endothelial dysfunction and increased reactive oxygen species, which induce inflammation and brain damage, and may cause brain iron deposition.[26] However, another previous study has shown that patients with HTN have significantly reduced susceptibility values in the RN and DN.[27] These findings intimate that the effect of HTN on brain iron redistribution may be more complex process. The dynamics in brain iron content of cerebral-cerebellum, white matter-gray matter, and other parts may be different and larger sampled studies are needed.

Iron homeostasis is essential for maintaining the normal function of the brain.[4] Excessive iron deposition has been found to be neurotoxic and to be related to various neurological diseases causing cognitive impairment.[4,6] Some animal experiments have shown that increased brain iron causes oxidative stress and neuron apoptosis, which may lead to neurodegeneration and cognitive dysfunction.[28,29] Additionally, ferroptosis may also play a role in these processes.[6] According to previous studies, MCI is related to iron deposition in certain brain areas, while more severe cognitive impairment like dementia may be related to more iron deposition in expanded brain areas.[29,30] A recent study has demonstrated that the iron concentration of deep gray matter affect the functional connectivity networks, thereby changing the cognitive performance.[31] Our results show that the iron content in the bilateral CN, PU, and DN of the HTN patients with MCI is significantly higher than that of the normal controls, and the iron content of the bilateral CN was significantly higher than that of the HTN patients without MCI. Given that there are no age or gender differences among the three groups, brain iron deposition in deep gray matter may be one of the causes of cognitive impairment in HTN patients.

Our results shows that the increased iron in the CN, PU, and GP of HTN patients with MCI are negatively correlated with the naming scores, delayed memory scores, and MoCA total scores. The basal ganglia including the striatum (CN, PU, GP) and other nuclei act in various cognitive processes, including executive function, learning, memory, emotion, motor control, and sensation function.[32] The striatum receives input information from the cortex and subcortical structures and projects it to various nuclei, and various neurological diseases such as ataxia and Huntington's disease are closely related to the pathological state of the striatum.[4,33] Lesions involving the CN cause cognitive impairment such as decreased executive function and slowed information processing,[34] and damage to the PU and GP is related to the decline in exercise performance, learning, and emotion.[33] A previous study has also demonstrated negative correlation

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TABLE 2. Susceptibility Values (ppb) Differences Among the Three Groups

ROI	Normal Controls	HTN, No MCI	HTN, With MCI	*P*-Value	*P*-Value (Post Hoc Analysis) A	B	C
Right CN	41 ± 12	42 ± 13	50 ± 15	0.015*	0.820	0.011*	0.019*
Left CN	39 ± 9	41 ± 13	51 ± 23	0.022*	0.770	0.014*	0.030*
Right GP	137 ± 33	140 ± 42	155 ± 51	0.222	0.841	0.122	0.177
Left GP	141 ± 31	139 ± 45	152 ± 50	0.435	0.818	0.351	0.233
Right PU	51 ± 9	59 ± 26	65 ± 24	0.044*	0.152	0.013*	0.318
Left PU	50 ± 12	60 ± 18	67 ± 19	0.001*	0.044*	0.001*	0.100
Right TH	−3 ± 7	−6 ± 7	−6 ± 11	0.271	0.220	0.121	0.814
Left TH	−3 ± 7	−8 ± 8	−6 ± 12	0.163	0.062	0.183	0.482
Right RN	135 ± 30	134 ± 27	138 ± 40	0.890	0.877	0.762	0.643
Left RN	133 ± 29	132 ± 32	134 ± 44	0.976	0.950	0.884	0.833
Right SN	144 ± 27	152 ± 29	158 ± 37	0.240	0.393	0.092	0.446
Left SN	147 ± 30	145 ± 31	152 ± 34	0.699	0.815	0.581	0.420
Right DN	116 ± 38	124 ± 26	140 ± 47	0.067	0.474	0.025*	0.131
Left DN	119 ± 36	124 ± 28	140 ± 41	0.079	0.589	0.034*	0.114
Right FWM	−10 ± 4	−9 ± 5	−10 ± 6	0.533	0.328	0.933	0.326
Left FWM	−10 ± 5	−9 ± 7	−10 ± 7	0.969	0.990	0.840	0.827
Right PWM	−10 ± 4	−9 ± 5	−8 ± 6	0.408	0.569	0.186	0.470
Left PWM	−9 ± 5	−7 ± 6	−7 ± 6	0.365	0.173	0.283	0.687
Right OWM	−19 ± 7	−16 ± 9	−19 ± 7	0.265	0.147	0.857	0.161
Left OWM	−17 ± 8	−16 ± 5	−18 ± 7	0.628	0.480	0.875	0.352

Susceptibility values for the three groups were compared using an ANOVA analysis. A = HTN without MCI vs. normal controls. B = HTN with MCI vs. normal controls. C = HTN with MCI vs. HTN without MCI.
*$P < 0.05$.

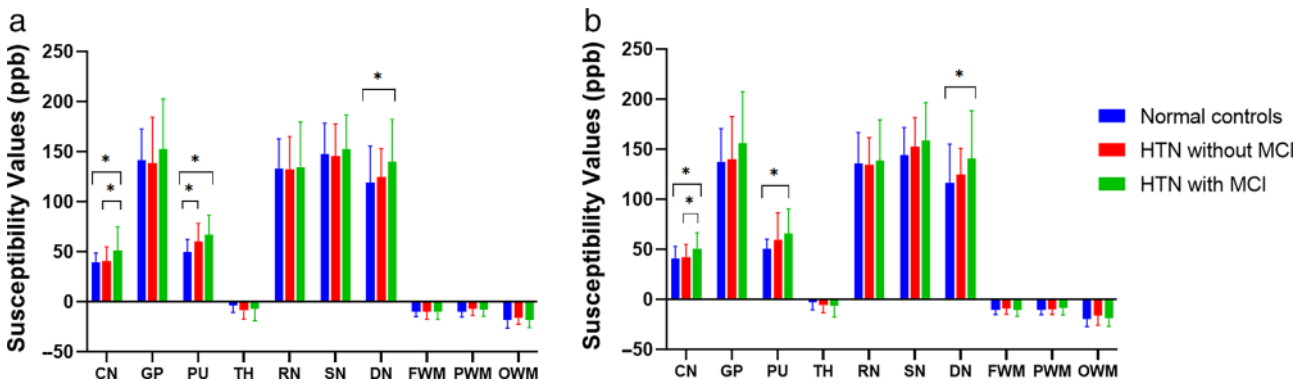

FIGURE 3: Susceptibility values (ppb) differences among the three groups. Significant differences among HTN without MCI group, HTN with MCI group and Normal controls are represented as *P < 0.05. a = left; b = right. MCI, mild cognitive impairment; HTN, hypertension; CN, caudate nucleus; GP, globus pallidus; PU, putamen; TH, thalamus; SN, substantia nigra; RN, red nucleus; DN, dentate nucleus; FWM, frontal white matter; PWM, parietal white matter; OWM, occipital white matter.

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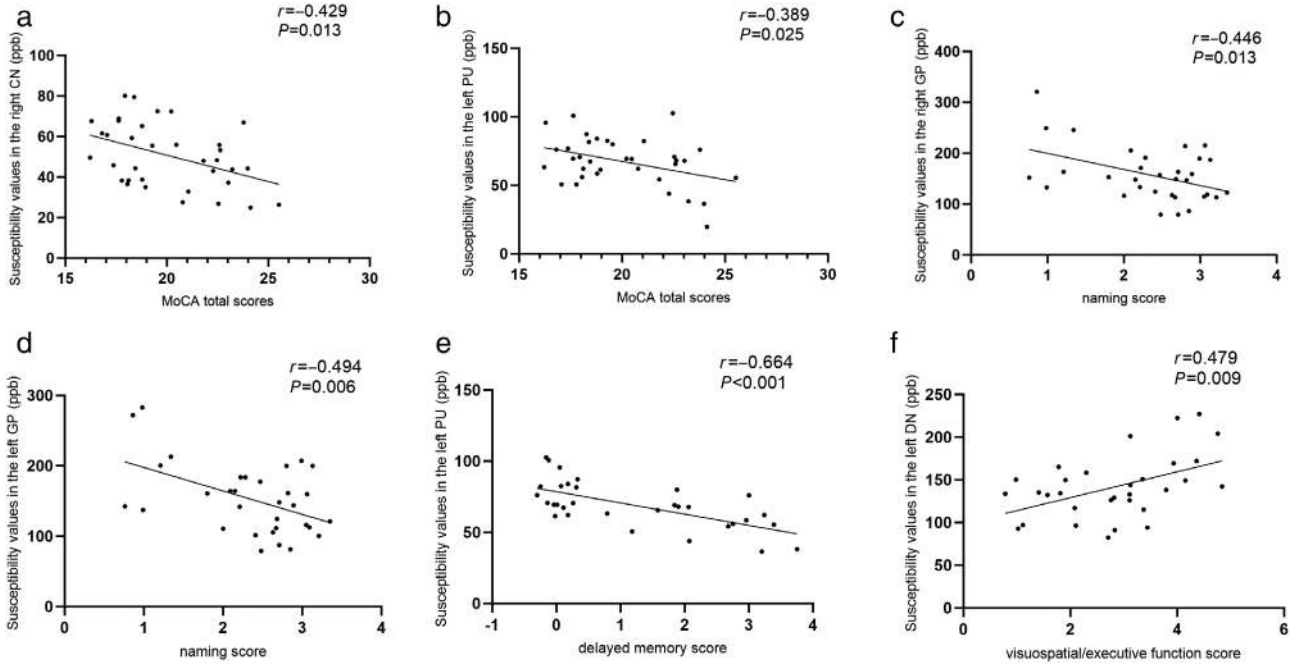

FIGURE 4: (a–f) Correlations between the susceptibility values in the ROI and the neuropsychological cognitive scores of the HTN with MCI patients. (a,b) Correlations between the susceptibility values in the right CN, the left PU, and the MoCA total score. (c,d) Correlations between the susceptibility values in the bilateral GP and the naming scores. (e) Correlations between the susceptibility values in the left PU and the delayed memory scores. (f) Correlations between the susceptibility values in the left DN and the visuospatial/executive function scores.

between iron deposition in the hippocampus, cortical areas, basal ganglia, and cognitive impairment.[29] Therefore, we speculate that iron deposition in the striatum of the HTN may damage neuronal function or disrupt connectivity, and then affect cognitive function in a number of ways. However, whether brain iron quantification can be used as a pathophysiological biomarker for cognitive impairment in HTN patient needs further study.

In this study, we also found that the susceptibility values of the left DN are positively correlated with the visuospatial/executive function score. The DN is the largest cerebellar nucleus and is one of the main channels for information transmission between the cerebellum and the midbrain, which affects functions of multiple cerebral–cerebellum connection circuits such as attention, executive control, emotion, and addiction.[35] Iron deposition in the DN is associated with neurodegenerative diseases such as ataxia.[36] However, it is not yet clear why iron deposition in the DN positively correlates with the visuospatial/executive function score in HTN. The cerebellum has the potential asymmetric hemispheric sensitivities for information processing,[37] and the DN plays a key role in the executive function, A previous study has demonstrated that executive function was significantly correlated with functional MRI activation in the right DN.[38] Thus, we speculate that altered iron distribution might affects cognitive function, and right DN's functional dominant might influence the correlation between iron deposition and visuospatial/executive function score. Nevertheless, larger-sample size studies are needed to clarify the underlying mechanism of the iron deposition's effect on cognitive status in HTN.

Limitations

Firstly, this preliminary cross-sectional study on brain iron alteration in HTN patients has a relatively small sample size, and does not represent all age groups. Previous studies have shown inconsistent effects of blood pressure on cognition in different aged patient groups.[2,39] Therefore, larger sampled size studies are needed. Secondly, this research focuses on the changes in iron deposition in the deep gray matter nuclei and white matter for HTN patients without and with MCI. We think a whole-brain voxel analysis might reveal more details of iron deposition and its effect on cognition. Thirdly, the neuropsychological tests we used are limited, and further comprehensive assessment on the subjects' cognitive status might assist the management of HTN patients. Finally, the significant changes are only on the order of 10–15 ppb and on average not that large relative to the baseline iron content. How such a low iron increase can affect cognition is unclear.

Conclusion

Increased susceptibility in bilateral CN, PU, and DN may indicate higher iron deposition in these regions in HTN patients. The significant correlation between susceptibility of the right CN, left PU, bilateral GP and the results of

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cognitive assessment may show the effect of iron deposition on cognitive impairment.

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