Assessing Mild Cognitive Impairment in Parkinson’s Disease by Magnetic Resonance Quantitative Susceptibility Mapping Combined Voxel-Wise and Radiomic Analysis

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Keywords
Parkinson’s disease · Mild cognitive impairment · Dementia · Quantitative susceptibility mapping

Abstract
Background: The relationship between iron accumulation in the central nervous system and cognitive decline in Parkinson’s disease (PD) has not been fully elucidated. This study aimed to explore the value of quantitative susceptibility mapping in assessment of mild cognitive impairment (MCI) in PD.

Methods: Sixteen PD patients with MCI (PD-MCI), sixteen normal cognition PD patients (PD-NC), and 28 healthy controls (HCs) were included. The differences in the magnetic susceptibility and Radiomic indicators among groups and their correlations with Montreal Cognitive Assessment-Basic (MoCA-B) scores and Unified Parkinson’s Disease Rating Scale Part III (UPDRS-III) were analyzed. Receiver operating characteristic curves were used to evaluate the diagnostic performance.

Results: Higher iron deposition was observed in the cortical and subcortical structures of the PD-MCI group compared with HCs, including limbic system, orbitofrontal cortex, cuneus, red nucleus, and substantia nigra. Combined magnetic susceptibility and texture index yielded the best diagnostic performance (area under curves: 0.828) in differentiating PD-MCI from PD-NC. The magnetic susceptibilities of the substantia nigra, red nucleus, putamen, globus pallidus, hippocampus, and thalamus were negatively correlated with the MoCA-B scores (all \( p < 0.05 \)), and of the putamen and amygdala were positively correlated with the UPDRS-III scores (both \( p < 0.05 \)).

Conclusion: Higher iron deposition was observed in the cortical and subcortical structures of the PD-MCI and PD-NC groups. The susceptibility values of vulnerable brain subregions shown significant correlation with MoCA-B and UPDRS-III. Together with the texture index, magnetic susceptibility values could provide robust performance in distinguishing PD-MCI patients from PD-NC.

Introduction
Iron accumulation in substantia nigra neurons and glial cells is a pathological feature of Parkinson’s disease (PD) [1]. The reaction of excessive iron with hydrogen...
peroxide to promote the generation of free radicals might be an important pathological mechanism of PD [2]. Quantitative susceptibility mapping (QSM) is a technique to measure magnetic susceptibility accurately and sensitively [3]. QSM-derived magnetic susceptibility has showed the involvement of iron in PD [4–6]. Moreover, the magnetic susceptibility of the dentate nucleus and red nucleus increased dramatically in PD patients with tremor, while the magnetic susceptibility of the caudate nucleus was associated with rigidity severity [7]. High magnetic susceptibility values were found in the cortex of PD with mild cognitive impairment (PD-MCI) patients than the normal cognition PD patients (PD-NC). The corresponding susceptibilities were further negatively correlated with the Montreal Cognitive Assessment (MoCA) scores [8]. Compared with non-demented PD patients, a higher concentration of iron deposition was observed in the hippocampus of PD patients with dementia (PDD). It was thus speculated that iron accumulation in the limbic structures was correlated with cognitive function [9]. Nevertheless, the relationship between iron accumulation in the central nervous system and cognitive decline in PD has not been fully revealed, the diagnostic efficacy of iron deposition for PD and PD-MCI has not been confirmed.

In addition, a loss of high signal associated with substantia nigra can distinguish healthy controls (HCs) from PD patients. The distribution of iron in these areas can also reflect the pathological changes of nigrostriatal in PD [8]. As PD involves spatially heterogeneous changes of iron distribution in the subcortical structure, textural features such as entropy, variance, and kurtosis may be useful for assessing the PD pathological changes [10]. First-order features of radiomic can extract local attributes reflecting the changes and distribution of iron deposition in the region of interest (ROI), and provide more detailed insight into iron deposition in the ROI. No research has yet incorporated the texture features of magnetic susceptibility mapping into a discriminant analysis of PD-MCI, PD-NC, and HCs. Therefore, this study aimed to explore the potential value of magnetic susceptibility as an imaging biomarker in assessing the cognitive decline in PD-MCI patients and analyze the correlation between the magnetic susceptibility index of ROI and the cognitive function score in the PD group.

Material and Methods

Study Design and Participants

This study is a cross-sectional study of idiopathic PD patients diagnosed according to the UK Parkinson Disease Society Brain Bank [11] at the Neurology Department of the Affiliated Hospital of Yangzhou University from August 2018 to October 2019. Twenty-eight healthy volunteers matched with PD patients for age and sex were also recruited as HCs.

The inclusion criteria were (1) 45–80 years, (2) Hoehn-Yahr (H-Y) scale ≤3, (3) clinical dementia rating score <1, and (4) right-handed. The exclusion criteria were (1) obvious lesions confirmed by previous medical history or routine MRI, (2) Parkinsonism-Plus syndrome, (3) significantly cognitive impairment, clinical dementia rating ≥1, (4) patients with poor image quality, or (5) patients with claustrophobia, in vivo metal implantation.

This study was approved by the Ethics Committee of the Affiliated Hospital of Yangzhou University (2017-YKL12-15). All patients signed the informed consents.

Clinical and Cognitive Function Assessment

Two senior PD-specialized neurologists (Dr. Liu, Dr. Xu) used the H-Y grade scale and the Movement Disorder Society-Unified Parkinson’s Disease Rating Scale (UPDRS) [13] to assess the patients and reached an agreement through discussions if their conclusions were inconsistent. The disease severity of all PD patients was assessed with the H-Y stage scale before MRI scanning. Their motor functions during the “off” state were assessed using the UPDRS Part III (UPDRS-III). The patients had to stop using anti-Parkinson’s drugs for at least 12 h before the clinical assessment and their previous medication was recorded and converted into levodopa equivalent daily dose.

The cognitive function of each subject was comprehensively assessed by specially trained personnel using the Chinese version of MoCA-Basic (MoCA-B) [14–16]. One point was added if education was <4 years, another point was added if the subject was illiterate. A subject with a total score of <26 was considered to have MCI.

Grouping

The PD patients were divided into PD-MCI and PD-NC groups. The PD-MCI group consisted of patients who met the diagnostic criteria for PD-MCI proposed by the International Parkinson and Movement Disorder Society (MDS) [17].

MRI Scanning

All MRI experiments were performed on a Discovery MR750W 3.0-T MRI scanner (GE Healthcare, Waukesha, WI, USA) with 16-channel head/neck combined coils. Before scanning, a sponge pad was used to fix the subjects’ head to prevent from motion artifacts. All subjects underwent three-dimensional fast spoiled gradient-recalled-echo, fluid-attenuated inversion recovery, spin-echo echo-planar-imaging based diffusion-weighted imaging, and multi-gradient echo-based QSM sequences. The parameters of each sequence and image analysis are shown in the online supplementary material (see www.karger.com/doi/10.1159/000522329 for all online suppl. material).

Statistical Analysis

In Statistical Parametric Mapping version 12 toolbox (http://www.fil.ion.ucl.ac.uk/spm/), the voxel-based statistics were analyzed by analysis of variance (ANOVA) and pairwise comparison among the PD-NC, PD-MCI, and HC groups. The significant p threshold of voxel-wise comparison was set to <0.01, and the false discovery rate (FDR) method was applied for multiple corrections (p < 0.05).
Numerical data statistical analyses were performed using SPSS 17.0 (SPSS Inc., Chicago, IL, USA). The continuous data were tested for normal distribution using the Shapiro-Wilk test. The homogeneity of variance was tested using Levene’s test. For normally distributed data, the differences were tested using Student’s t test among the two groups and single-factor ANOVA among the three groups. For non-normally distributed data, the Kruskal-Wallis H test was used to compare differences among the three groups and the Mann-Whitney test was used to compare differences between every two groups. Categorical data were described as n (%) and
tested using the $\chi^2$ test. Receiver operating characteristic curves and area under the curve (AUC) was used to evaluate the diagnostic performance of each indicator with statistical differences. Additionally, Pearson’s correlation coefficient was used to evaluate the relationship between the magnetic susceptibility in ROIs and the MoCA or UPDRS-III scores. $p < 0.05$ was considered significant.

Results

Characteristics of the Participants

Demographics and results of the neuropsychiatric assessments are tabulated in (Table 1). Participants were matched for age, gender, and educational level. A total of 16 patients in the PD-MCI group, 16 patients in the PD-NC group, and 28 patients in the HC group were included in this study. Significant difference was found in MoCA score between the PD-MCI and PD-CN groups ($p < 0.001$) (Table 1).

Voxel-Wise Comparisons of the Magnetic Susceptibility Map

The voxel-wise comparisons of the QSM value showed significant differences in several regions (Fig. 1; online Suppl. Table 1). One-way ANCOVA showed significant group differences. Post hoc analysis revealed susceptibility increases of PD group compared with HC group in substantia nigra, inferior temporal gyrus (right), middle frontal gyrus (right), etc. In addition, widespread absolute susceptibility increases in PD-MIC compared with PD-NC. Voxel-based analyses showed significant differences of magnetic susceptibility among the three groups in parahippocampal gyrus (left), substantia nigra, tractus rubrospinalis, superior frontal gyrus, orbital part (right), insula (right), middle occipital gyrus (left), middle frontal gyrus (right), cuneus (left), median cingulate and paracalangulate gyrus, and supramarginal gyrus (left) ($p < 0.05$, FDR correction, Fig. 1a; online suppl. Table S1). PD group had higher susceptibility than the HC group in the parahippocampal gyrus (left), substantia nigra, tractus rubrospinalis, inferior temporal gyrus (right), inferior frontal gyrus, triangular part (right), middle frontal gyrus (right), and precentral gyrus (right) ($p < 0.05$, FDR correction, Fig. 1b; online suppl. Table S1). The PD-MCI group showed higher susceptibility than the PD-NC group in the fusiform gyrus (left), cerebellum (left), hippocampus, superior frontal gyrus, dorsolateral (right), thalamus, median cingulate and paracalangulate gyrus (left), postcentral gyrus (left), and inferior parietal supramarginal gyrus (left) ($p < 0.05$, FDR correction, Fig. 1c; online suppl. Table S1).

ROI Analysis of Mean Magnetic Susceptibility Values

The mean QSM values and Radiomic features of the ROI-based analysis were summarized in (Fig. 2; Table 2). Vulnerable regions based on PD pathological analyses, such as the substantia nigra and the entorhinal cortex, may be too small to be reliably assessed using voxel-based analysis; however, these areas showed significant susceptibility and Radiomic feature changes in the ROI-based analysis. Indicators with statistical differences between groups were shown in Figure 2. ANOVA revealed significant main effect for group in magnetic susceptibility of substantia nigra (F2, 59 = 5.545, $p = 0.006$), red nucleus (F2, 59 = 3.188, $p = 0.049$), hippocampus (F2, 59 = 4.186, $p = 0.020$), thalamus (F2, 59 = 3.961, $p = 0.025$), and amygdala (F2, 59 = 3.688, $p = 0.031$). Post hoc $t$ test further showed differences between two groups in substantia nigra: PD-MCI versus HC groups ($p = 0.002$); red nucleus: PD-MCI versus HC groups ($p = 0.014$); putamen: PD-MCI versus PD-NC groups ($p = 0.045$); parahippocampal gyrus: PD-MCI versus HC groups ($p = 0.018$); cuneus: PD-MCI versus HC groups ($p = 0.047$); amygdala: PD-MCI versus HC groups ($p = 0.009$); thalamus: PD-MCI versus HC groups ($p = 0.039$), hippocampus: PD-NC versus PD-MCI groups ($p = 0.007$), PD-MCI versus HC groups ($p = 0.031$); orbitofrontal cortex: PD-NC versus PD-MCI groups ($p = 0.048$); thalamus: PD-NC versus PD-MCI groups ($p = 0.009$); and globus pallidus: PD-MCI versus HC groups ($p = 0.045$) (Fig. 2; Table 2).

Radiomic ANOVA

ANOVA revealed significant main effect for group in variance of substantia nigra (F2, 59 = 3.313, $p = 0.044$). Regions with differences between two groups: substantia nigra: PD-MCI versus HC groups ($p = 0.013$); entorhinal cortex: PD-NC versus HC groups ($p = 0.044$); thalamus: PD-MCI versus HC groups ($p = 0.005$), PD-NC versus PD-MCI groups ($p = 0.019$); and putamen: PD-NC versus PD-MCI groups ($p = 0.047$), PD-NC versus HC groups ($p = 0.019$), and PD-MCI versus HC groups ($p = 0.005$) (Fig. 2; Table 2).

Radiomic Analysis of Kurtosis

ANOVA revealed significant main effect for group in kurtosis of the entorhinal cortex (F2, 59 = 4.002, $p = 0.024$) and the cuneus (F2, 59 = 5.759, $p = 0.005$). Regions with differences between two groups: entorhinal cortex: PD-NC versus PD-MCI groups ($p = 0.031$) and PD-NC versus HC groups ($p = 0.009$); precentral: PD-NC versus PD-MCI groups ($p = 0.036$) and PD-MCI versus HC groups ($p = 0.036$); cuneus: PD-MCI versus HC groups

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Fig. 2. a The differences in mean magnetic susceptibility values are based on the ROI analysis. b The differences in variance values based on ROI analysis. c The differences in kurtosis values based on ROI analysis. d The differences of skewness values based on ROI analysis.
Table 2. Mean magnetic susceptibility value, variance, kurtosis, and skewness values among the three groups

|                           | PD-NC | PD-MCI | HC     | PD-NC | PD-MCI | HC     | PD-NC | PD-MCI | HC     | PD-NC | PD-MCI | HC     | PD-NC | PD-MCI | HC     |
|---------------------------|-------|--------|--------|-------|--------|--------|-------|--------|--------|-------|--------|--------|-------|--------|--------|
| Substantia nigra          | 0.057±0.009 | 0.062±0.012 | 0.052±0.009 | 0.00211±0.00192 | 0.00299±0.00309 | 0.00143±0.00079 | 2.901±0.808 | 2.830±0.673 | 2.770±0.495 | 0.122±0.581 | 0.071±0.627 | −0.010±0.519 |          |
| Red nucleus               | 0.050±0.008 | 0.056±0.016 | 0.047±0.010 | 0.00099±0.00050 | 0.00158±0.00212 | 0.00088±0.00056 | 3.031±0.676 | 2.761±0.544 | 2.700±0.490 | −0.021±0.526 | −0.025±0.426 | −0.181±0.341 |          |
| Putamen                   | 0.031±0.006 | 0.037±0.010 | 0.032±0.007 | 0.00059±0.00026 | 0.00088±0.00050 | 0.00065±0.00041 | 4.891±1.671 | 4.694±1.656 | 4.753±2.116 | 1.214±0.429 | 1.159±0.309 | 1.156±0.286 |          |
| Globus pallidus           | 0.037±0.007 | 0.063±0.014 | 0.056±0.010 | 0.00141±0.00034 | 0.00201±0.00129 | 0.00195±0.00238 | 3.338±0.990 | 3.745±1.162 | 3.802±1.363 | 0.387±0.305 | 0.530±0.451 | 0.591±0.523 |          |
| Hippocampus               | 0.023±0.001 | 0.026±0.003 | 0.024±0.003 | 0.00033±0.00006 | 0.00041±0.00111 | 0.00038±0.00008 | 8.890±4.166 | 7.403±2.136 | 8.098±3.721 | 1.776±0.487 | 1.578±0.264 | 1.666±0.446 |          |
| Parahippocampal gyrus     | 0.025±0.003 | 0.027±0.004 | 0.024±0.003 | 0.00051±0.00022 | 0.00054±0.00117 | 0.00044±0.00013 | 12.185±8.025 | 8.729±2.751 | 10.493±5.477 | 2.089±0.817 | 1.780±0.312 | 1.921±0.551 |          |
| Orbitofrontal cortex      | 0.024±0.005 | 0.028±0.005 | 0.025±0.004 | 0.00066±0.00023 | 0.00077±0.00028 | 0.00066±0.00016 | 8.874±3.358 | 7.190±2.178 | 8.169±2.861 | 1.903±0.331 | 1.661±0.313 | 1.772±0.262 |          |
| Entorhinal cortex         | 0.032±0.009 | 0.032±0.007 | 0.028±0.006 | 0.00084±0.00038 | 0.00076±0.00024 | 0.00061±0.00023 | 9.729±6.720 | 6.689±2.466 | 6.425±1.891 | 1.852±0.787 | 1.524±0.423 | 1.512±0.292 |          |
| Thalamus                  | 0.024±0.002 | 0.027±0.004 | 0.025±0.003 | 0.00046±0.00009 | 0.00055±0.00015 | 0.00045±0.00011 | 16.097±5.010 | 13.508±3.377 | 14.030±4.171 | 2.645±0.540 | 2.205±0.467 | 2.384±0.446 |          |
| Fusiform gyrus            | 0.019±0.002 | 0.020±0.002 | 0.019±0.002 | 0.00036±0.00007 | 0.00035±0.00008 | 0.00033±0.00007 | 12.952±4.624 | 11.612±2.081 | 11.439±2.810 | 2.251±0.365 | 2.177±0.221 | 2.085±0.304 |          |
| Precuneus                 | 0.020±0.002 | 0.021±0.002 | 0.020±0.002 | 0.00048±0.00014 | 0.00055±0.00021 | 0.00052±0.00019 | 6.074±4.237 | 4.145±1.045 | 5.849±3.149 | 1.126±0.456 | 0.871±0.242 | 1.010±0.470 |          |
| Cuneus                    | 0.019±0.002 | 0.019±0.002 | 0.018±0.002 | 0.00036±0.00009 | 0.00036±0.00009 | 0.00036±0.00008 | 11.589±3.321 | 10.294±2.169 | 13.106±3.110 | 2.252±0.272 | 2.099±0.303 | 2.462±0.369 |          |
| Amygdala                  | 0.030±0.004 | 0.032±0.005 | 0.029±0.004 | 0.00058±0.00016 | 0.00061±0.00017 | 0.00054±0.00019 | 5.789±2.485 | 5.287±1.482 | 5.560±1.992 | 1.332±0.364 | 1.284±0.330 | 1.349±0.356 |          |
| Caudate head              | 0.030±0.004 | 0.031±0.005 | 0.032±0.005 | 0.00048±0.00014 | 0.00055±0.00021 | 0.00052±0.00019 | 6.074±2.337 | 4.145±1.045 | 5.849±3.149 | 1.126±0.456 | 0.871±0.242 | 1.010±0.470 |          |

PD-MCI, Parkinson’s disease with mild cognitive impairment; PD-NC, Parkinson’s disease with normal cognition; HC, healthy control.
$r = -0.388, p = 0.028$

$r = -0.468, p = 0.007$

$0.015 0.020 0.025 0.030 0.035$

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$MoCA$
**Diagnostic Performance of ROI with Indicators of Difference**

While magnetic susceptibility showed a good performance in hippocampus with high sensitivity of 75%, specificity of 68.7%, and AUC of 0.813 \( (p = 0.003) \), a combination of susceptibility and texture index provided higher sensitivity of 87.5%, specificity of 75%, and AUC of 0.828 \( (p = 0.002) \), (Fig. 3).

**Correlation Analyses**

Regions showing significantly negative correlations with MoCA-B scores were the substantia nigra \( (r = -0.388, p = 0.028) \), red nucleus \( (r = -0.423, p = 0.016) \), putamen \( (r = -0.468, p = 0.007) \), globus pallidus \( (r = -0.403, p = 0.022) \), hippocampus \( (r = -0.486, p = 0.005) \), and thalamus \( (r = -0.541, p = 0.001) \). Those having significantly positive correlations with UPDRS-III scores were the putamen \( (r = -0.369, p = 0.038) \) and amygdala \( (r = -0.351, p = 0.049) \) (Fig. 4).

**Discussion**

This study showed that the PD group had high magnetic susceptibility values in the substantia nigra, tractus rubrospinalis, parahippocampal gyrus (left), inferior temporal gyrus (right), inferior frontal gyrus triangular part (right), middle frontal gyrus (right). A previous study has also reported an increase in susceptibility in the frontal cortex and temporal lobe of PD patients [18]. Using a whole-brain voxel-based approach, another study detected widespread QSM perturbations across the cuneus, precuneus, fusiform gyrus, orbitofrontal cortex, cerebellum exterior, and insula [8]. In our study, we found that the PD-MCI group had significantly higher magnetic susceptibility than did the PD-NC group in the inferior parietal supramarginal gyrus (left); postcentral gyrus (left); median cingulate (left); Thalamus, Hippocampus, fusiform gyrus (left); superior frontal gyrus, dorsolateral (right); middle frontal gyrus (right). Regions such as fusiform gyrus and inferior parietal supramarginal gyrus were consistent with previous studies [8]. In a previous study, the PD-MCI group had higher magnetic susceptibility in the posterior cortical areas, including the bilateral cunei, than the PD-CN, and HC groups [8]. These changes might be related to posterior cortical hypometabolism, which induces visual dysfunction and is a risk factor for dementia in PD patients [19]. Another study showed that the magnetic susceptibility of the prefrontal lobe and orbitofrontal cortex in the PD-MCI group increased compared with other groups, and such regions were often related to emotional and cognitive functions [18].

In this study, the PD-MCI group had notably higher magnetic susceptibility than the PD-NC group in the substantia nigra, red nucleus, bilateral putamen, parahippocampal gyrus, cuneus, and amygdala. There is an increase in the magnetic susceptibility of the substantia nigra, red nucleus, thalamic nucleus, and globus pallidus nucleus in PD patients [20]. The neurodegenerative process underlying PD in the basal ganglia of the gray matter nuclei contributes additively to the effect of iron deposition, which renders susceptibility more sensitive to pathological tissue changes than R2* mapping. Specifically, the results involving the substantia nigra, red nucleus, thalamus nucleus, and globus pallidus nucleus were consistent in most studies [21]. The most remarkable basal ganglia effect was that an apparent magnetic susceptibility increases consistently with iron deposition in the dorsal substantia nigra tightly concordant with known PD distributions of α-synuclein pathology [6]. In radiomic analysis, the variance index of magnetic susceptibility map of substantia nigra was higher than control group; this was consistent with previous research results [10]. The increase of variance reflects the heterogeneous changes of iron deposition in the substantia nigra. In patients with PD, the nigral degeneration progression starts in nigro-some-1 and then spreads to the matrix and other nigro-somes [22]. We presumed that the heterogeneous distribution of iron deposition might reflect the different progression of PD-MCI and PD. Similarly, the red nucleus serves as an essential intersection between primary and cerebellar motor pathways [23]. Multiple studies have shown that the magnetic susceptibility of the red nucleus is significantly increased in PD patients [24]. It is speculated that it may reflect increased iron deposition owing to PD-related oxidative stress and neuromelanin oversaturation [25]. In addition, the significant negative correlation between iron deposition in the substantia nigra, red nucleus, and globus pallidus and the MoCA score. The correlation between the red nucleus and substantia nigra and cognition was not significant in a previous study [7].

In this study, magnetic susceptibility of the putamen in the PD-MCI was higher than that of the PD-NC group and was no significant difference between PD-NC and HC groups. Iron deposition in putamen was supported by a postmortem study that showed positive results in increasing the iron deposition in the nucleus [26]. However, unlike previous studies, we found significant differences in PD-MCI but did not detect significant differences in PD-NC and HC [8, 27]. A recent study also found...
an increase of magnetic susceptibility in PD patients, and it is speculated that there might be a pattern of increasing iron deposition in the GP-FN-SN pathway [24]. The controversy may arise because of variations of iron levels according to the subregions of the putamen and the iron migration through unclear pathways between different brain regions during the progression of PD. Meanwhile, the radiomic analysis results showed that the variance of the bilateral putamen was significantly different among the three groups. Increased iron metabolism was observed in the PD-MCI group of our study, and this increase was rather nonuniform, in contrast, iron was more evenly distributed in PD-NC group than in other groups. A postmortem study [26] has shown that the accumulation of calcium and magnesium in the putamen nucleus increases with age. Consequently, further research is needed to investigate the specific mechanism whether the increased magnetic susceptibility is caused by the pathological process of PD.

In this study, the magnetic susceptibility of the thalamus was significantly different between the PD-MCI and HC groups and between the PD-MCI and PD-NC groups. This finding was different from previous studies. In a study on PDD, the magnetic susceptibility of the right thalamus in non-demented PD patients was higher than the HC group, while the PDD group did not show any significance after the post hoc test [8]. Our results revealed that the iron distribution in bilateral thalamus of the PD-MCI group was more uneven than the other groups, and the skewness was lower. Such a distribution pattern shows that iron accumulation in the thalamus is spatially heterogeneous, and this distribution pattern is particularly significant in the PD-MCI group.

Similarly, the magnetic susceptibility of the hippocampus was significantly different between the PD-MCI and HC groups and between the PD-MCI and PD-NC groups. A previous study on PDD showed increased iron concentration in the bilateral hippocampus and right thalamus, and increased iron concentration in the left hippocampus compared with PD patients without dementia. Besides, the iron content of the bilateral hippocampus was found to be moderately correlated with both cognitive function and psychotic symptoms [9]. A correlation analysis revealed the magnetic susceptibility of the hippocampus and thalamus increased with the decrease of MoCA [18]. Our finding of susceptibility changes in the hippocampal regions of PD patients may reflect increased pathological levels of Alzheimer’s disease in these regions. In addition, the combination of susceptibility and texture index in hippocampus has achieved the best diagnostic value. These results suggested that the susceptibility and texture index could be used as effective imaging biomarkers in assessing the cognitive decline in PD-MCI patients.

Finally, an ROI-based QSM analysis showed that the limbic system exhibited significantly higher susceptibility values in the PD-MCI group [8]. Similar to that previous study [8, 27], we found a positive correlation between the putamen and the severity of motor deficit, but on the other hand, we found a positive correlation between iron deposition in the amygdala and the severity of motor deficit. In addition, different from their results, we found that there was a negative correlation between iron deposition in putamen and MoCA score. The plausible involvement of iron deposition in the amygdala and putaminal structure in developing PD’s motor symptoms is suggested.

This study has some limitations. First, the cognitive function score by the MoCA scale only is subjective to some extent, and the assessment of each sub-function may not be precise. Second, this study divided the PD group into two subgroups of PD-MCI and PD-CN, which resulted in a small sample size in each group. The next step will be expanding the sample size. Finally, this study was based on cross-sectional setting. We plan to carry out a longitudinal study in the future to reveal the neuropathological mechanism of cognitive impairment in PD.

In conclusion, higher iron deposition was observed in the cortical and subcortical structures of the PD-MCI and PD-NC groups. Apart from the red nucleus and substantia nigra, a higher iron deposition was observed in the limbic system, orbitofrontal cortex, cuneus, and other regions of the PD-MCI group. A combination of susceptibility values and texture index could be used as effective imaging biomarkers to discriminate PD-MCI patients. In addition, it was found that there were correlations between iron content and cognitive impairment in some regions of PD patients.

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Statement of Ethics

This study was approved by the Ethics Committee of the Affiliated Hospital of Yangzhou University (2017-YKL12-15). All patients signed the informed consents before the MRI examination.
Conflict of Interest Statement

All authors declare that they have no competing interests.

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Author Contributions

Yi Zhao and Hang Qu conceived and coordinated the study; designed, performed, and analyzed the experiments; wrote the paper. Wei Wang, Jiangbing Liu, Yu Pan, Zheng Li, Gang Xu, and Chunhong Hu carried out the data collection and data analysis and revised the paper. All authors reviewed the results and approved the final version of the manuscript.

Data Availability Statement

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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