Application of high-field magnetic resonance imaging in Parkinson's disease

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Abstract. The present study aimed to observe the structural changes of the extracorticospinal tract in Parkinson's disease (PD) using susceptibility-weighted imaging (SWI) and diffusion tensor imaging (DTI) magnetic resonance (MR) scans. The association of DTI parameters and brain-iron accumulation with PD was examined and imaging signs useful in the diagnosis of PD were explored. The study included 30 patients with PD and 30 age- and gender-matched healthy controls who underwent routine MR, SWI and DTI scans. The corrected phase (CP) values of the substantia nigra (SN), red nucleus (RN), globus pallidus (GP) and putamen (PUT) were measured, and fractional anisotropy (FA) and apparent diffusion coefficient (ADC) values were obtained. Significant differences were found in the CP values between the PD and control groups in the SN, RN and PUT, but there were no differences in other regions of interest (ROIs). The FA values of the SN and PUT in the PD group were significantly decreased compared with those of the control group, but there was no significant difference in the FA values of the GP. Furthermore, there was no significant inter-group difference in the ADC values of any ROIs. In conclusion, SWI is a method useful for evaluating brain-iron deposition in PD. Increasing iron storage levels have previously been shown to be associated with PD pathogenesis but not with the degree of PD severity. FA values may be useful for diagnosing PD, and DTI may offer some insight into PD pathomechanisms and clinical diagnosis.

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Introduction

Parkinson's disease (PD) is an insidious neurodegenerative condition that is difficult to diagnose as its early symptoms are easily confused with those of Parkinson's syndrome, Parkinson-plus syndrome and idiopathic tremor (1). Over time, the pathogenic mechanisms of PD cause severe damage to dopaminergic neurons in the midbrain, and clinical symptoms are difficult to control (2).

Single-photon emission computed tomography (SPECT) and positron emission tomography scans (PET) are the most sensitive and specific methods for diagnosing PD and evaluating treatment efficacy (3). However, they are difficult to implement in clinical practice as they are expensive and use high doses of radiation. In recent years, more powerful magnetic resonance imaging (MRI) technology, particularly functional MRI, has offered more sensitive signals, sharper images of brain structures, and information concerning microscopic features and physiological metabolism. These new MRI methods have the ability to provide new insights into PD (4). The present study aimed to explore new methods of early PD diagnosis and treatment evaluation using susceptibility-weighted imaging (SWI) and diffusion tensor imaging (DTI).

Iron deposition increases in the brain of patients with PD, predominantly in the form of ferritin and particularly in oligodendrocytes, in addition to in neurons and microglia (5). Typical sites of iron deposition include the globus pallidum, substantia nigra, and the red and dentate nuclei. Ferritin is paramagnetic; therefore, SWI filtered-phase images are particularly suitable for showing increased iron content in the brain (6). Abnormally elevated iron levels are evident in many neurodegenerative disorders, including PD (7).

Materials and methods

Patients. The present study included 30 right-handed patients with PD (12 males and 18 females) who were examined at the Affiliated Hospital of Inner Mongolia Medical University (Hohhot, China) between April 2013 and March 2015. The ages of the patients ranged from 58 to 74 years with a mean of 67.17 years. The range of disease duration was from 4.6 to 11 years with a mean of 6.89 years. Unilateral symptomatic
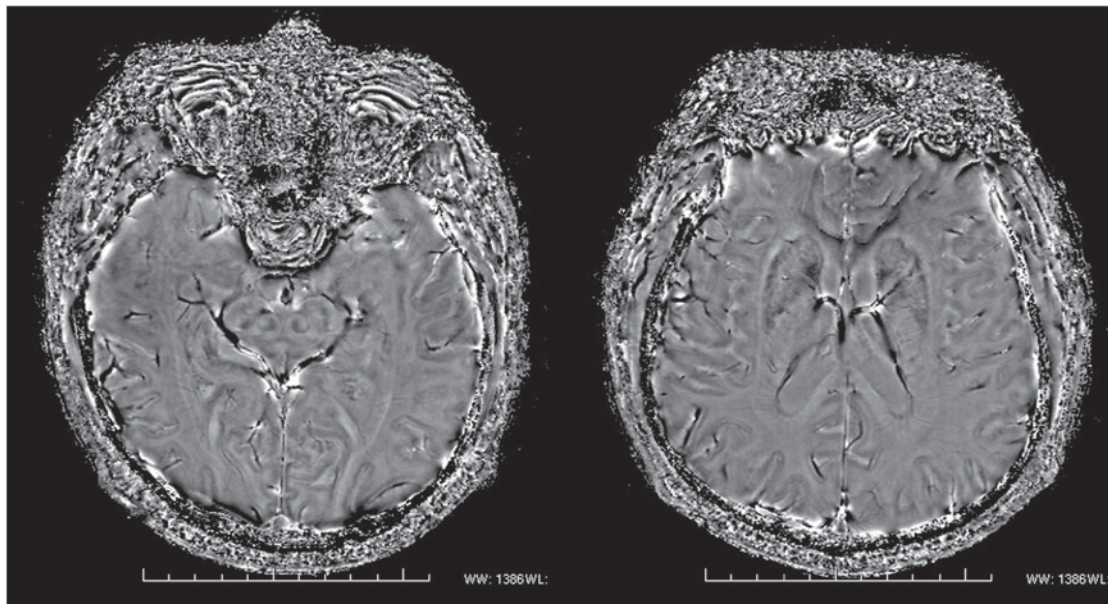
Figure 1. Corrected phase diagrams from the susceptibility-weighted imaging of a patient with Parkinson's disease. The substantia nigra, red nucleus, globus pallidus and putamen exhibited low signals, which indicated iron deposition, with bilateral symmetry, and the regions without iron deposition exhibited relatively high signals.

patients graded 1.0-1.5 with the Hoehn and Yahr rating scale (8) were included in the PD group. The PD group was compared with 30 healthy age- and gender-matched individuals in the normal control (NC) group. The present study was approved by the Ethics Committee of Inner Mongolia Medical University and informed consent was obtained from each participant.

Imaging. MRI data were collected using a 3.0-Tesla scanner (GE Signa HDx; GE Healthcare, Milwaukee, WI, USA). Conventional scanning included axial T2-weighted imaging (T2WI)-periodically rotated overlapping parallel lines with enhanced reconstruction (PROPELLER), diffusion-weighted imaging (DWI), T1-weighted imaging (T1WI) and sagittal T1WI to exclude cerebral hemorrhage or infarction.

SWI scanning was performed using gradient echo type echo planar imaging (GRE-EPI) sequences [field of view (FOV), 24x24 cm; matrix, 448x438; flip angle, 20°; repetition time (TR) 32 msec; echo time (TE), 20 msec] with whole-brain coverage using 64 axial 2-mm slices with 0-mm spaces between the slices.

DTI images were also taken (FOV, 24x24 cm; matrix, 128x128; whole brain coverage; flip angle, 138°; TR, 10,000 msec; TE, 9,518 msec] using 25 directions, and 4-mm slices with 0-mm spaces between the slices.

Image processing. For SWI, the region of interest (ROI) was manually delineated, and the phase values were measured on the corrected phase diagram (Fig. 1). The layer showing the areas of interest most clearly and the adjacent upper and lower layers were selected, and then the ROI was manually delineated based on the outlines of different brain regions to obtain the corrected phase (CP) values. Finally, the mean value was calculated.

DTI was conducted according to anatomy; the ROIs were drawn in the layer that showed the biggest, clearest ROI, and

the fractional anisotropy (FA) and apparent diffusion coefficient (ADC) values were measured concurrently (Fig. 2).

Image quality assessment. Two experienced radiologists independently observed the SWI sequence magnitude diagrams; evaluated the signal contrast between the midbrain, basal ganglia nuclei, and the surrounding tissues, as well as the boundary clarity; and then compared them with conventional T2WIs and T1WIs to evaluate image quality.

Statistical analysis. Gaussian distribution tests and homogeneity tests for variance were used to compare the PD and NC groups. The CP, FA and ADC values of the ROIs in the bilateral substantia nigra (SN), red nucleus (RN), globus pallidus (GP) and putamen (PUT) were calculated using independent sample t-tests. The mean values for each hemisphere were calculated separately. Finally, the CP, FA and ADC values of different brain regions were compared between the two groups. SPSS version 14.0 software (SPSS, Inc., Chicago, IL, USA) was used for all analyses, and $P<0.05$ was considered to indicate a statistically significant difference.

Results

Image quality assessment. The results of image quality assessment showed that the small gray matter nuclei were displayed more clearly in the magnitude diagrams than in the corrected phase diagram and DTI, and the midbrain and basal ganglia nuclei were detectable in the magnitude diagrams. Furthermore, the reduced signal intensities in the PD group indicated that there was significant iron deposition in the nuclei of the PD group in comparison with the NC group (Fig. 3).

CP value comparisons. The CP values of the SN, RN and PUT in the PD group were significantly different from the
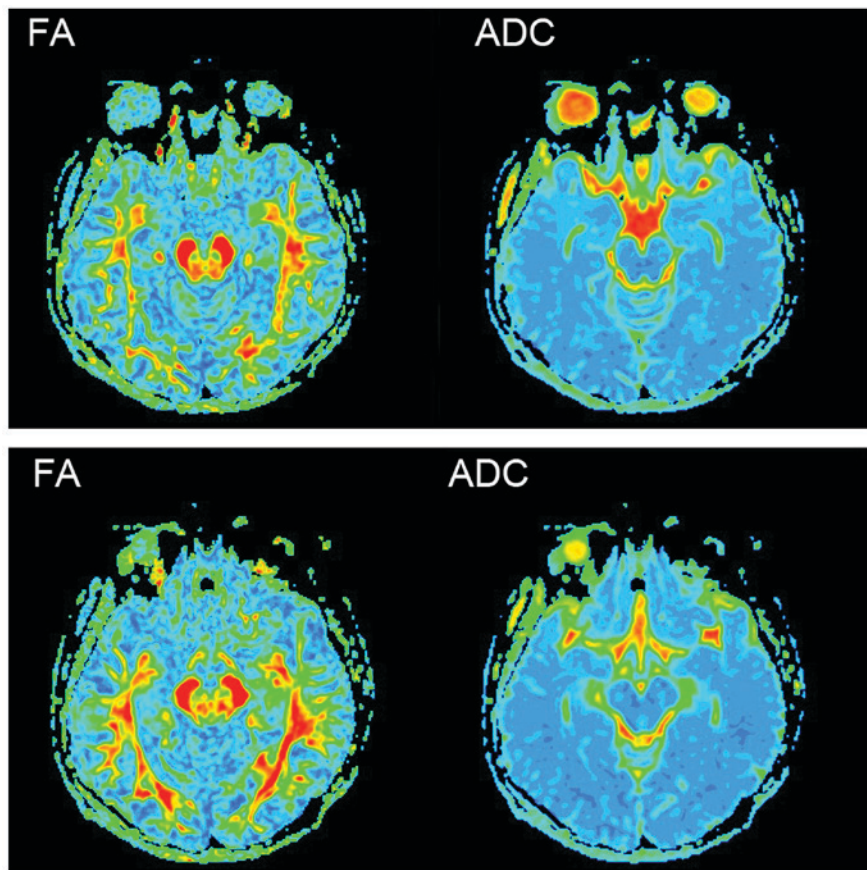
Figure 2. Fractional anisotropy (FA) and apparent diffusion coefficient (ADC) maps from the diffusion tensor imaging of a patient with Parkinson's disease. Upper images show the substantia nigra (SN) and red nucleus (RN), and lower images show the globus pallidus (GP) and putamen (PUT). Regions of interest including the SN, RN, GP and PUT regions were identified and data measured.
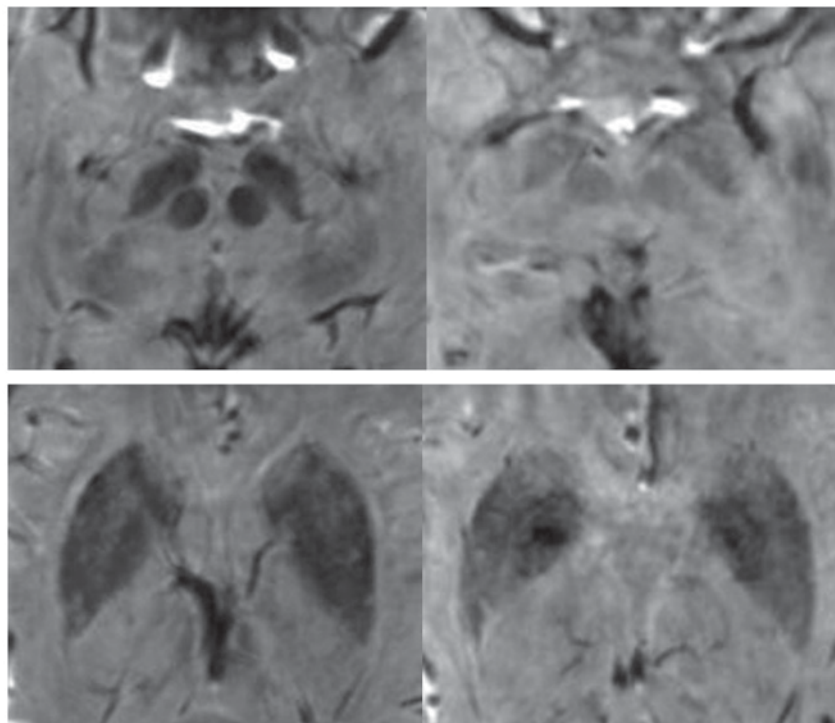

Figure 3. Susceptibility-weighted imaging magnitude diagram. Upper images show the substantia nigra (SN) and red nucleus (RN), and lower images show the globus pallidus (GP) and putamen (PUT). Images on the left are from a male patient, 67 years old, with Parkinson's disease, who had stiff limbs and involuntary upper limb tremor for 2 years, particularly on the left side, and showed unclear articulation when agitated. The RN, SN, GP and PUT signals were significantly reduced in this patient compared with an age- and gender-matched healthy control (right side images), suggesting that there was severe iron deposition and significant narrowing of the pars compacta of the SN.

Table I. Comparison of CP values between healthy controls and patients with PD (mean ± standard deviation).

Brain region	NC group	PD group	t	P-value
SN	1,940.735±18.021	1,871.619±61.924	-3.410	0.002
RN	1,969.810±36.901	1,854.905±73.138	-4.502	<0.001
GP	1,948.959±17.092	1,903.532±84.312	-1.913	0.075
PUT	2,014.891±35.997	1,954.218±37.235	-3.786	0.001

CP, corrected phase; PD, Parkinson's disease; NC, normal control; SN, substantia nigra; RN, red nucleus; GP, globus pallidus; PUT, putamen.

Table II. Comparison of FA values between healthy controls and patients with PD (mean ± standard deviation).

Brain region	NC group	PD group	t	P-value
SN	0.650±0.071	0.374±0.095	-5.013	<0.001
RN	0.434±0.060	0.494±0.215	2.089	0.052
GP	0.412±0.054	0.367±0.088	-0.958	0.319
PUT	0.271±0.045	0.291±0.029	-3.069	0.004

FA, fractional anisotropy; PD, Parkinson's disease; NC, normal control; SN, substantia nigra; RN, red nucleus; GP, globus pallidus; PUT, putamen.

Table III. Comparison of the ADC values between healthy controls and patients with PD (mean ± standard deviation).

Brain region	NC group	PD group	t	P-value
SN	8.426±0.241	8.503±0.649	0.204	0.814
RN	6.842±0.462	7.066±0.797	0.962	0.346
GP	8.123±0.353	8.314±0.396	1.475	0.191
PUT	7.465±0.290	7.589±0.372	1.582	0.143

ADC, apparent diffusion coefficient; PD, Parkinson's disease; NC, normal control; SN, substantia nigra; RN, red nucleus; GP, globus pallidus; PUT, putamen.

corresponding values of the control group (all P<0.05). Specifically, the CP values in all three locations were significantly decreased, and the iron deposition increased, compared with those in the control group. There was no significant difference between the PD and control groups in the CP values of the GP (P>0.05; Table I).

FA and ADC value comparisons. The FA values of the SN and PUT in the PD group were observed to be significantly decreased compared with those in the control group (P<0.05). However, there was no significant difference in the FA value of the GP (P>0.05; Table II), and there were no significant inter-group differences for any of the ADC values (P>0.05; Table III).

Discussion

PD is primarily characterized by striatonigral pathway degeneration; dopamine (DA) and acetylcholine (Ach) signaling are compromised during the subclinical stage, but the patient might not exhibit symptoms due to striatal compensations, including increased DA receptor sensitivity and enhanced neuronal excitability (9). It has been reported that patients with PD manifest clinical symptoms when 50% of dopaminergic neurons in the SN are lost (10), which indicates that pathological changes in the SN occur prior to overt disease. This underscores the need to develop effective methods to monitor pathological changes in the SN and design early interventions for PD.

A growing body of research indicates that abnormal brain iron deposition occurs in several neurodegenerative conditions including PD, multiple system atrophy, multiple sclerosis, and Alzheimer's disease (11). *In vivo* measurement of brain iron concentrations might therefore be helpful for the diagnosis of these diseases and for predicting the prognoses of patients.

In the present study, SWI magnitude diagrams and phase diagrams showed significantly weaker signals in the SN, RN, GP and posterolateral PUT for the PD group compared with the control group, suggesting increased iron deposition in these regions. Conventional MRI confirmed uneven brain iron distributions.

The CP values of the SN, RN and PUT were significantly decreased in the PD group compared with the NC group, but

there was not a significant difference in CP values of the GP between the two groups. This indicates that pathological iron deposition was more severe in SN, RN, and PUT. This result is also consistent with a previous study (12), and confirms the inhomogeneity and region selectivity of PD-related brain iron deposition. Excessive iron ions catalyze reactions that induce oxidative stress, ultimately generating free radicals that selectively damage dopaminergic neurons in the SN (13). However, it is unclear whether iron deposition in these sites directly induces PD mechanisms. Further investigation of abnormal iron deposition in these areas might clarify the pathogenesis and clinical symptom progression of PD.

SWI is able to detect abnormal iron deposition in extrapyramidal gray nuclei (14). As mentioned above, abnormal iron levels are not unique to PD. A number of neurodegenerative diseases are characterized by abnormal increases in brain iron content; however, the deposition sites vary in different diseases (15). Iron deposition has also been shown to occur in the cerebrovasculature, particularly in elderly patients (3). It has been hypothesized that the increase in brain iron content might be due to age-associated micro bleeds that lead to the deposition of hemosiderin (16), and it cannot be excluded that increased iron levels in the PD-affected brain are due to this phenomenon. In addition, CP values might also be affected by other materials with high magnetic susceptibility. For the reasons cited above, it is necessary use other methods in combination with SWI to provide more accurate and objective data. The use of DTI for PD has improved in recent years; changes in microscopic tissue structure and function can be sensitively detected, allowing accurate monitoring of the SN and other brain regions affected in PD.

The main pathological characteristic of PD is degeneration of striatonigral pathways. The SN is the brain area that is most seriously damaged in this disease (17); dopaminergic neuron loss is most evident in the pars compacta region of the SN. Yoshikawa *et al* (18) described significantly decreased FA values for the striatonigral pathway projection fibers (connecting the SN and the lower part of the striatum) and SN of patients with PD. The results of the present study are consistent with this. FA is a measure of the diffusion anisotropy of water molecules and can be used quantify the integrity of neuron membranes and myelinated fibers, as well the arrangement of white matter tracts (19). The decreased FA values in the SN of PD patients might be due to: i) Ferritin deposition affecting dopaminergic neuron function, ii) axonal dysfunction or loss of dopaminergic neurons in the SN, iii) microglia proliferation-induced disorder in white matter fiber arrangement and/or structure, and/or iv) multiple factors influencing reduced anisotropy of the local tissue (20). The neuropathological changes in the SN of PD patients are partially due to the aforementioned reasons. In the present study, significant differences in FA values of the SN between the PD and NC groups were identified, suggesting that changes in neuronal structure or function can be detected early in the disease. Therefore, FA values of the SN could be used as a diagnostic biomarker of subclinical or early PD. Yoshikawa *et al* (18) proposed that more than half of dopaminergic neurons in the striatonigral projection system have already died when PD symptoms develop. Therefore, DTI could be helpful in providing earlier

diagnoses and maximizing the treatment window. Changes in SN microstructure in early PD patients can be reflected by abnormal FA values since decreased FA is negatively correlated with disease progression.

It is hypothesized that decreased FA values in the context of neurodegenerative disease might be associated with neuronal loss, reactive astrocyte proliferation, and axon demyelination, and other factors (21). Thus it is necessary to identify specific factors that lead to changes in FA. According to the principles of DTI, changes in tissue susceptibility, for example, increased iron content in SN, could significantly alter diffusion signals. In the present study, the average CP value was positively linearly correlated with the FA value of the SN but not that of the PUT in the PD group. This finding suggests that reduced FA was associated with increased iron content in the SN. It also suggests that pathological PD changes can be monitored by a combination of DTI and SWI. These modalities could also be helpful in the clinical diagnosis of PD.

ADC values reflect the rate of diffusion of extracellular water molecules in a gradient field. No statistically significant differences in the mean ADC values of the ROIs between the PD and NC groups were identified in the present study (all $P>0.05$), which was consistent with the results from another study (22). These results suggest that ADC is not sufficiently sensitive to detect microscopic structural changes in brain tissue. However, Schocke *et al* (23) reported that although there was no statistically significant difference in the ADC values of basal ganglia and SN between PD patients and controls, the ADC values tended to be elevated in patients with more advanced PD. They therefore concluded that ADC could be useful for assessing microscopic structural changes in extrapyramidal and motor function areas.

In conclusion, the diagnosis and assessment of PD primarily relies on clinical symptoms, and objective evidence is lacking. High-field MRI is a simple, effective, sensitive, and noninvasive screening method that can assess abnormal iron deposition based on CP values and quantitatively assess FA values of basal nuclei. Therefore, it could provide a basis for exploring PD pathogenesis and examining pathophysiological changes over time. Such information could serve as an objective reference for the clinical diagnosis of PD, thus guiding treatment and improving patient prognosis.

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