

Original Article

DTI and ESWAN sequences are effective for the early diagnosis of Parkinson's disease

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Abstract: The present study is to investigate the properties of modifications in substantia nigra (SN) pars compacta in early stages of Parkinson's disease (PD) by quantitatively analyzing fractional anisotropy (FA) and T2* values of SN pars compacta. Twenty patients diagnosed with early PD from March 2012 to February 2013 were included in the present study. A 1.5 T magnetic resonance imaging (MRI) system with an eight-channel head coil was used to obtain images. Diffusion tensor imaging (DTI) and enhanced T2 star weighted angiography (ESWAN) sequences were conducted. FA and T2* values were separately measured and statistically analyzed. Compared with control, the values of FA and T2* in rostral, middle, and caudal areas of SN were decreased significantly in subjects who were diagnosed with early PD. Moreover, no significant difference in T2* value was observed between groups or within any group. Compared with T2*, FA values in the rostral area of SN pars compacta were decreased significantly, being a potential values in the early diagnosis of PD. The present study demonstrates that FA values are more sensitive and accurate than T2* values in identifying PD, and are more valuable in the early diagnosis of PD compared with T2* values. With the improvement of MRI technology and continuous understanding of PD, new MRI technology will play crucial roles in the diagnosis of early PD.

Keywords: Magnetic resonance imaging, Parkinson's disease, DTI, diffusion tensor imaging, fractional anisotropy, ESWAN

Introduction

Parkinson's disease (PD) is a degenerative disease of the nervous system. Patients who are diagnosed as PD are commonly middle aged individuals. PD has a chronic progressive development, with the main feature of detected degeneration of dopaminergic neurons in the substantia nigra (SN) and nigrostriatal pathways. Moreover, dopamine quantity in basal ganglia demonstrates a close correlation with the severity of the disease. It is reported that the clinical symptoms of PD appear to be more than 50 percent loss of dopaminergic neurons in the SN. This is an indication that the clinical symptoms occur after pathological changes in the SN [1]. Therefore, the diagnosis of early PD is important for the future treatment of the patients. A non-invasive method is required to

effectively and efficiently observe the pathological modifications in SN and basal ganglia. In addition, treating PD in time can improve the patient's quality of life and enhance the value of prognosis.

Diffusion tensor imaging (DTI), based on diffusion-weighted imaging, is performed to quantitatively analyze the diffusion velocity and direction of water molecules in three dimensions and to evaluate the integrity and continuity of the organizational structure. Dopaminergic cell degeneration and glial cell proliferation occur in PD, lead to changes in structures and functions in the corresponding regions, and are reflected by changes in FA values. Currently, DTI is applied in a large amount of studies regarding PD. Yoshikawa et al. report that the loss of dopaminergic neuronal function reaches 70%-80% in

the early stages of PD, which is accompanied by changes in FA values [1]. The decrease of FA values may reflect dopaminergic nervous degeneration, which is consistent with pathological findings. Most early studies have reported reduced FA in early PD patients [2-4]. Vaillancourt et al. observe that the fractional anisotropy (FA) value derived from 3.0 T magnetic resonance (MR) in the caudal SN in PD patients is lower than that in normal subjects, with a virtual sensitivity and specificity of 100% [1]. Consequently, DTI has become a non-invasive tool to quantitatively measure FA values in the SN, and can provide a more sensitive way to diagnose and estimate the early state of PD. However, Schwarz et al. have shown negative results of nigral FA measurements at regional, sub-regional, and voxel levels in conjunction with the results of meta-analysis of nigral FA changes [5]. Iron deposition is increased in the substantia nigra of PD [6, 7]. In addition, some evidence has demonstrated that iron deposition is correlated with disease stage in PD [8]. Enhanced T2 star weighted angiography (ESWAN) is based on the magnetic susceptibility differences in brain tissues [7, 9, 10]. ESWAN phase-weighted imaging can clearly show the nonheme iron with higher tissue contrast [1]. In the present study, DTI and ESWAN sequences are applied on SN pars compacta to find a new method for the early diagnosis of PD. We focus on evaluating the diagnostic accuracy of nigral DTI and ESWAN, and determining whether nigral diffusion metrics (FA) and T2* can qualify as candidate biomarkers.

Method and materials

Patients

Twenty patients (9 males and 11 females; aged from 54 to 83 years, with a mean age of 68.38 years) diagnosed with early PD from March 2012 to February 2013, were included in the present study. The participants were consistent with the diagnostic criteria derived from a literature [11]. For control, 28 healthy individuals (14 males and 14 females; aged from 53 to 82 years, with a mean age of 67.84 years) who were matched in sex and age were recruited. All procedures were approved by the Ethics Committee of Qinhuangdao Municipal No. 1 Hospital. Written informed consents were obtained from all patients or their families.

All patients were diagnosed with PD by a neurologist in movement disorders and met the PD Society Brain Bank Diagnostic Criteria. The diagnostic criteria included the reduction of movement and at least one of the following characteristics: muscle rigidity, rest tremor or postural instability, not caused by non-primary visual, vestibular, and proprioceptive cerebellar dysfunction. According to Hoehn and Yahr, the patients ranked I to II stage (equivalent to 0-50 scores in Unified Parkinson's Disease Rating Scale). In addition, effective treatment was observed in the subjects, after levodopa experimental treatment of one course.

If the signs and symptoms of PD were due to brain trauma, patients who were excluded did not meet certain criteria such as cerebrovascular disease, brain tumor, viral infection, or other neurological diseases. Patients who had contact with antipsychotic drugs, dopamine depletion drugs, or explicitly neurotoxin were also excluded. Moreover, observations were not made for the following signs: obvious supranuclear, visual movement disorders, cerebellar syndrome, nuclear dysphonia, orthostatic hypotension, changing over 30 mmHg, pyramidal system damage, and muscle atrophy. Otherwise, the patients were not considered for the research. For healthy controls, the exclusion criteria included the observation of brain trauma, cerebrovascular disease, brain tumor, viral infection, or carbon monoxide poisoning.

Magnetic resonance imaging (MRI)

A 1.5 T MRI system (GE Signa EXCITE, Little Chalfont, UK) with an eight-channel head coil was used to obtain images by running examinations including Sagittal T1WI, coronal T1WI, axial T2WI, DTI, and ESWAN. A fast spin echo sequence was applied to obtain sagittal and coronal T1-weighted images with the following parameters: TR/TE = 1875/16 ms, thickness = 7 mm, space = 1 mm, and slice number = 15. This was to obtain axial FSE-T2 sequence with TR/TE = 4500/102 ms. For DTI, the following parameters for acquisition included: TR/TE = 1000/84.5 ms, and 25 diffusion gradient directions with $b = 1000 \text{ s/mm}^2$; for ESWAN sequence, TR/TE = 27/20 ms, matrix = 256×256 , slice thickness = 3.0 mm, space = 0, and b value = 1000 s/mm^2 . The scanning of the brain's sagittal and coronal T1WI was first con-

Table 1. Differences of FA and T2* values in the substantia nigra pars compacta between PD and control groups

Positions	PD	Control group
Rostral substantia nigra	0.201 ± 0.030	0.254 ± 0.050
Middle substantia nigra	0.293 ± 0.048	0.364 ± 0.053
Causal substantia nigra	0.262 ± 0.030	0.298 ± 0.050

Note: Inter-group comparisons [$F(1, 46) = 54.90, P < 0.001$], intra-group comparisons [$F(2, 92) = 65.44, P < 0.001$], inter-group \times intra-group [$F(2, 92) = 1.94, P > 0.05$]. $P < 0.001$ in the rostral, middle and caudal areas by paired test. PD, Parkinson's disease.

Table 2. Comparison of FA values in the medial and lateral substantia nigra pars compacta between PD and control groups

Positions	PD	Control group
Medial	0.256 ± 0.037	0.300 ± 0.032
Lateral	0.252 ± 0.025	0.307 ± 0.034

Note: Inter-group comparisons [$F(1, 46) = 57.53, P < 0.001$], intra-group comparisons [$F(2, 92) = 0.03, P > 0.05$], inter-group \times intra-group [$F(2, 92) = 0.668, P > 0.05$]. PD, Parkinson's disease.

ducted with the orientation of T2WI set as vertical to the brainstem in coronal. Sagittal segments were obtained from anterior to posterior, which was referred to as the AC-PC line, and was represented as top line. A total of 20 continuous scanning slices were obtained without any interval (slice thickness of 3 mm) and covered the entire midbrain, pons, and most parts of the medulla oblongata. DTI sequence replicated the thickness, layer spacing, and the number of layers from T2WI sequence. ESWAN sequence replicated the scanning scope and the direction of T2WI.

Data were acquired using a DTI pulse sequence designed to reduce eddy current induced by distortion. In order to offset the eddy current effects and limit the maximal image shift and distortion to a subpixel level, the pulse sequence was capable of dynamically adjusting the imaging gradients and receiver frequency. The corrected image and T2WI image underwent fusion to select the layer demonstrating the clearest SN pars compacta. After amplification, the SN pars compacta was outlined manually. Six regions of interest (ROIs) were selected. From rostral SN pars compacta to caudal, six ROIs were selected, with each ROI area being 8 mm².

Merging FA values of ROIs 1-2, 3-4, and 5-6, and the rostral, middle, and caudal FA values of the SN pars compacta were acquired. After clearing the previous ROIs, nine circular ROIs (each equal to 4 mm²) were placed from the rostral to caudal in two rows. The FA values in the SN pars compacta were acquired through merging FA values of interior and lateral ROIs 1-9 separately. The selection and measurement of ROIs were completed by three experienced radiologists. The measurements of T2* values followed the same procedure as above.

Statistical analysis

SPSS 13.0 statistical package (IBM, Armonk, NY, USA) was used for statistical analysis. The data were expressed as means \pm SD. Factorial design analysis of variance methods were applied to compare inter-group difference of FA and T2* values. The significance threshold was set at $P < 0.05$. The scatters were plotted to demonstrate FA and T2* values of the rostral, middle, and caudal in the SN pars compacta, with linear correlation analysis being applied. Receiver operating characteristic (ROC) curves were applied to compare the sensitivity and specificity of FA and T2* values of SN pars compacta between PD and normal control group. The threshold value was set by conducting ROI curve analysis of the FA value in the rostral, middle, and caudal of the SN pars compacta between PD and control groups. All data were processed by three experienced radiologists and an average estimate was calculated in the process.

Results

FA values in rostral and middle areas of SN pars compacta are significantly lower than caudal FA value

To determine FA efficacy, DTI was performed. The total FA value in the early PD group was lower than control group ($P < 0.001$) (**Table 1**). The FA values of bilateral SN pars compacta were decreased in the rostral, middle, and caudal areas ($P < 0.001$) (**Table 1**). No significant difference was observed between the medial and lateral areas in the SN in early PD group ($P > 0.05$) (**Table 2**). The rostral, middle, and caudal areas under the ROC curve were 0.814, 0.818 and 0.786, respectively. The areas under the ROC curve of rostral and middle ROI were

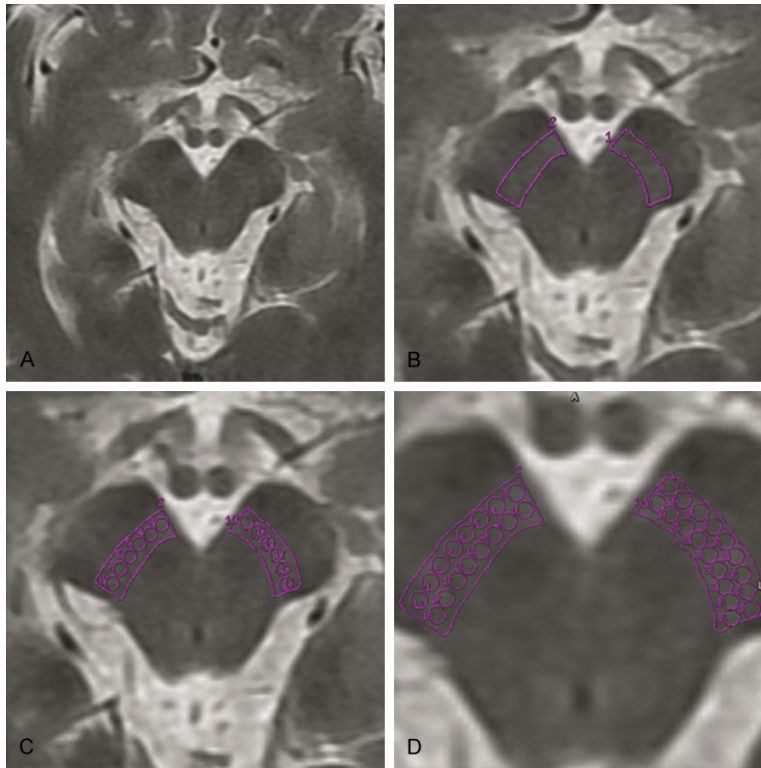


Figure 1. T2WI images. A. Substantia nigra pars compacta shown on magnified T2WI. B. Entire ROIs shown on fusion images. C. Six ROIs in the part of the substantia nigra pars compacta. D. Eighteen ROIs in the lateral substantia nigra pars compacta.

Table 3. Comparison of T2* values in different positions of substantia nigra pars compacta between PD and control groups

Positions	PD	Control group
Rostral substantia nigra	51.25 ± 4.26	55.24 ± 4.55
Middle substantia nigra	49.95 ± 3.30	54.46 ± 5.53
Causal substantia nigra	59.83 ± 3.44	63.88 ± 5.80

Note: Inter-group comparisons [$F(1, 46) = 27.51, P < 0.001$], intra-group comparisons [$F(2, 92) = 58.80, P < 0.001$], inter-group × intra-group [$F(2, 92) = 0.044, P > 0.05$]; Paired comparison $P_{(\text{Head} \times \text{body})} > 0.05, P_{(\text{Head} \times \text{tail})} < 0.001, P_{(\text{Tail} \times \text{body})} < 0.001$. PD, Parkinson's disease.

Table 4. Comparison of T2* values in the medial and lateral substantia nigra pars compacta between the PD and control groups

Positions	PD	Control group
Medial	58.43 ± 8.10	59.36 ± 4.12
Lateral	55.32 ± 6.23	56.52 ± 4.57

Note: Inter-group comparisons [$F(1, 46) = 0.823, P > 0.05$], intra-group comparisons [$F(2, 92) = 6.32, P > 0.05$], inter-group × intra-group [$F(2, 92) = 0.014, P > 0.05$]. PD, Parkinson's disease.

larger than that of the caudal part (**Figure 1**). Moreover, FA values of the rostral, middle, and caudal ROI were decreased by 20.9%, 19.5% and 12.1%, respectively, compared with normal control group. These results suggest that FA values in rostral and middle areas of SN pars compacta are significantly lower than caudal FA value in patients who are diagnosed with early PD.

T2 values in SNc in PD patients are significantly different from control group*

To test the efficacy of T2* values, ESWAN was employed. The T2* values of the rostral, middle and caudal areas in the SN pars compacta in early PD were significantly different from those observed in control group, especially in rostral and middle SN (**Table 3**). T2* values were not significantly different between medial and

lateral areas in SN between groups or within group (**Table 4**). As shown in scatter plot of bilateral T2* and FA values, there was no significant tendency of correlation between T2* and FA values in the SN in the overall study groups (both PD and control groups) (**Figure 2**). These results indicate that T2* values in SNc in PD patients are significantly different from control group.

Discussion

As a useful diagnostic tool, FA value is measured and statistically analyzed in SN pars compacta of early PD patients and control group. In the present study, FA values of bilateral SN pars compacta are lower in early PD group than those in control group. The decrease was identified in rostral, middle, and caudal areas. These results were consistent with previous findings [11, 12]. The possible reasons may be that the diffusion of water molecules is affected in the SN pars compacta due to the occurrence of dopaminergic cell degeneration,

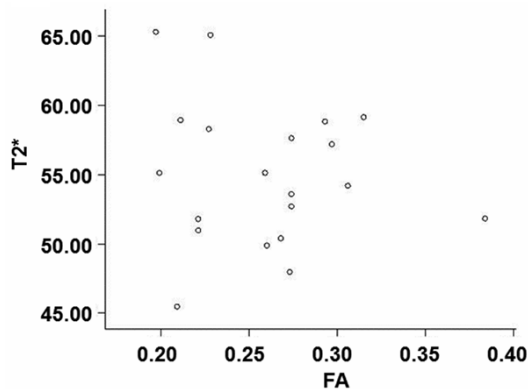


Figure 2. Scatter plot of bilateral FA and T2* values in patients with Parkinson's disease.

which results in decrement of FA values in the early stages of PD [2]. Observation shows that FA values in the rostral area of SN pars compacta are decreased, being inconsistent with the report by Vaillancourt et al. [1]. Dopaminergic neurons are mainly concentrated in SN pars compacta. However, Vaillancourt et al. have investigated an ensemble of the rostral area of SN, SN reticulata, and part of cerebral pedunculus fiber. Therefore, the results of Vaillancourt et al. cannot fully reflect SN dopaminergic neurons in the rostral area. The present study has overcome this deficiency by fusion DTI and T2WI images to provide a more convincing result. Moreover, there is no significant difference on FA values in the medial and lateral part of SN pars compacta between early PD group and control group ($P > 0.05$). The loss of dopaminergic cells in the ventrolateral part of the SN pars compacta is confirmed by autopsy in a previous study [3]. However, our results suggest no structural difference between the medial and lateral parts of SN pars compacta in patients with early PD.

Further results of PD show that iron deposition in SN may cause the degeneration and necrosis of dopaminergic neurons. It is reported that brain iron metabolism is disordered and iron level is increased significantly in PD [1]. Susceptibility weighted imaging phase-weighted imaging can clearly reflect tissue contrast, especially nonheme iron [1]. The T2* value was inversely proportional to iron content, with smaller T2* value representing higher iron content. Some scholars have observed that T2* values of SN in PD are significantly lower than control group [10, 13, 14]. This suggests that

the presence of pathological iron deposition in SN is positively correlated with the staging of PD [1]. Therefore, T2* values are used to refine SN pars compacta and to investigate the relationship between T2* values and early PD.

T2* value, as another diagnostic index, is measured and statistically analyzed in SN pars compacta of early PD patients and control group in the present study. The results indicate that there is significant difference between PD patients and control group in SN pars compacta, especially in rostral and middle SN. Furthermore, no statistical significance is observed in T2* values between medial and lateral areas in SN between groups or within a group. The T2* values of the rostral, middle, and caudal areas in SN pars compacta in early PD are significantly different from those in control group, especially in rostral and middle SN. This result demonstrates that abnormal iron deposition in early PD occurs mainly in rostral and middle SN. The asymmetry of iron deposition in SN pars compacta further illustrates that iron distribution in early stages of PD is not uniform. No significant difference in T2* values is observed between medial and lateral areas of SN pars compacta ($P > 0.05$), indicating no significant difference in iron deposition in the corresponding areas. In addition, increased iron deposition in SN pars compacta compared with control group is observed in the progression of PD.

FA and T2* values are both reduced in bilateral SN pars compacta, especially in the rostral and middle areas, and no significant difference is observed between medial and lateral areas ($P > 0.05$). It is noticed that FA values in bilateral head of SN pars compacta are decreased in PD group. Therefore, FA values are more sensitive and accurate than T2* values in identifying PD from control, and are more valuable in the early diagnosis of PD compared with T2* values. One limitation of the present study is the limited number of samples. Further study recruiting more subjects may reduce errors caused by individual differences. In conclusion, with the improvement of MRI technology and continuous understanding of PD, new MR technology will play crucial roles in the diagnosis of early PD.

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Disclosure of conflict of interest

None.

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