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Asymmetrical diffusion tensor imaging indices of the rostral substantia nigra in Parkinson's disease

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ABSTRACT

Objective: Motor asymmetry in Parkinson's disease (PD) is evident clinically and on functional neuroimaging, but not reported in diffusion tensor imaging (DTI). We aim to determine if asymmetry in fractional anisotropy (FA) and apparent diffusion coefficient (ADC) can be detected in the substantia nigra (SN) of PD subjects.

Methods: DTI scans were performed on 11 PD and 12 healthy subjects. Regions of interest (ROIs) were drawn by 2 independent raters at the caudal, middle and rostral SN on each side. FA and ADC were extracted from the ROIs.

Results: Significant asymmetry was observed in the FA ($p < 0.005$) and ADC ($p < 0.00005$) at the rostral SN of PD subjects. The differences in FA and ADC across the left and right rostral SN were significantly different between PD and healthy subjects, $p < 0.05$ and $p < 0.02$ respectively. PD subjects had significantly higher ADC at the left rostral SN than healthy subjects ($p < 0.01$). Significant correlation between the Unified Parkinson's Disease Rating Scale (UPDRS) motor scores and the FA was noted in the left rostral SN ($r = 0.7$, $p < 0.03$).

Conclusions: Asymmetry in DTI indices was noted at the rostral SN of PD subjects. The relationship between FA in the SN and UPDRS motor score was studied. Our findings may provide a model for better understanding of the implication of FA reduction in the SN.

1. Introduction

Parkinson's disease (PD) is a neurodegenerative disorder characterized by nigrostriatal cell loss, resulting in striatal dopamine deficiency [1]. The motor symptoms such as bradykinesia, rigidity, and tremor appear when 80% of the striatal dopamine, or 50% of the nigral cells are lost [1,2]. In general, one side of the body is affected more than the other, and the asymmetry persists throughout the course of the disease [3,4]. Motor asymmetry is correlated with contralateral striatal dopamine deficiency [5] and contralateral ventricular enlargement [6]. However, the reason for the asymmetrical involvement is not known.

Diffusion tensor imaging (DTI) is a relatively new technique to study the fibre tracts in the brain through measurement of the directional and diffusivity of water molecules [7]. Fractional anisotropy (FA) and apparent diffusion coefficient (ADC) are two measurable DTI values which give the directionality (anisotropy) and magnitude (diffusivity) of water diffusion respectively [8].

The FA is a scalar value between 0 and 1, with higher values found in white matter due to orientation and organization of the fibres [9,10]. A breakdown in fibre integrity should result in a lower FA due to isotropic flow, and a higher ADC due to increase magnitude of water diffusion. Various studies have reported a lower FA in the substantia nigra (SN) of PD subjects, and along the nigrostriatal projections into the frontal lobes, the premotor areas and the cingulum [11,12]. One group has shown a trend towards higher ADC in the SN of PD subject [11]. Changes in FA can reveal the progressive degeneration in the SN and the ascending nigrostriatal fibres [11,13]. Using high resolution DTI, reduced FA has been shown in the caudal, middle and rostral regions of the SN in early untreated PD patients, with high sensitivity and specificity in the caudal regions [13]. In a study on PD subjects on medication, Modrego et al. [14] found a significant correlation between the Unified Parkinson's Disease Rating Scale (UPDRS) motor score and the FA at the side of the rostral SN with a lower mean value, which indirectly suggests a possible asymmetry of FA at the rostral SN.

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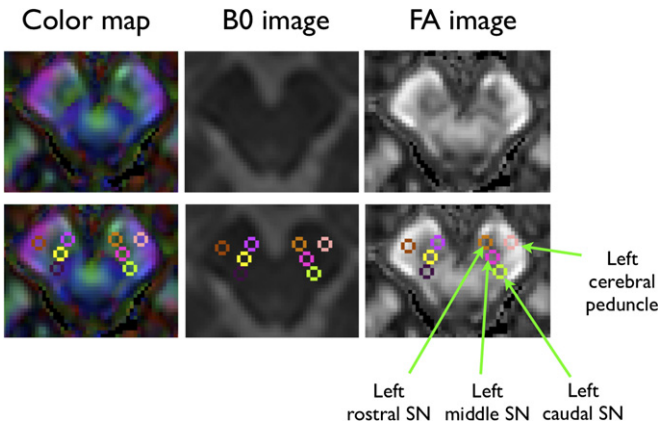

Fig. 1. ROI locations of a typical PD subject as seen on the colour, B0 and FA image.

However, significant asymmetry for FA or ADC in the SN of PD subjects has never been reported in the literature to date.

In this study, we aim to determine if asymmetry in FA and ADC can be detected in the SN of PD subjects in the early stages of the disease. The relationship between motor severity and the DTI indices is also studied.

2. Methods

We studied 11 clinically definite PD subjects (7 women, 4 men, mean age 60.4 ± 9.3 years) according to the diagnostic criteria of Calne et al. [3] and 12 normal subjects (6 women, 6 men, mean age 60.8 ± 8.5 years). All were right handed ethnic Chinese. Subjects with atypical parkinsonism, dementia, psychiatric illness, severe motor fluctuation, on dopamine blocking agents, or with contraindications to magnetic resonance imaging were excluded from the study. The PD subjects had mild to moderate disease severity with Hoehn and Yahr Stage (HY) 1–3 and mean UPDRS motor score of 23.5 ± 9.5, and average disease duration of 5.7 ± 4.2 years. There were five PD subjects with clinically most affected side on the right, five PD subjects with clinically most affected side on the left, and one PD subject with symmetrical clinical involvement. All PD subjects underwent the DTI scanning after overnight withdrawal of antiparkinson medication for at least 12 h. The study was approved by the Institution Ethics and Review Board. All subjects gave written informed consent to the study.

DTI in 16 directions was performed on a 3 T MRI system (Achieva 3.0, Philips Medical Systems, Best, The Netherlands) using single shot, spin-echo echo planar imaging (EPI) sequence; b-value of 0 and 800 s/mm^2; repetition time (TR), 4500 ms; echo time (TE), 60 ms; flip angle, 90°; number of averages, 1; reconstructed matrix = 256 × 256; slice thickness 3 mm with no gap; field of view (FOV) 230 × 230 mm; voxel size = 0.9 × 0.9 × 3 mm^3. DTI scans were performed 3 times per subject to improve the signal-to-noise ratio. DTI signal processing was performed using DTIStudio version 3.0.3 [15].

We used the regions of interest (ROI) method as described by Vaillancourt et al. [13], with two independent raters (BDP, WLA). Each ROI was 3.59 mm in diameter. ROIs were placed on the caudal SN, middle SN, rostral SN and cerebral peduncle (Fig. 1). The FA was extracted from the cerebral peduncle as a control procedure to ensure correct placement of ROI at the rostral SN [13,16]. Both FA and ADC were extracted from each of the 6 ROIs placed over the SN for each subject. The mean FA and mean ADC at each ROI, across all 6 SN ROIs, and the difference between the left and right SN ROIs were calculated for each subject group. Unpaired *t*-tests were used for comparisons across subject groups, and paired *t*-tests for comparisons within subject group. Correlation analysis was performed between the DTI indices and various factors such as age, disease duration, and UPDRS motor score. The sample size was too small for multivariate analysis. Statistical analyses were performed in R version 2.13.0 [17].

3. Results

There were no significant differences in the extracted FA and ADC at each respective ROI locations between the two raters (BDP, WLA). As such only values obtained by WLA were reported in this paper.

3.1. DTI asymmetry

Table 1 shows the mean FA and ADC at the SN of PD and normal subjects. There was a non-significant trend towards lower FA and higher ADC amongst PD subjects compared to healthy controls. The FA at the left SN was significantly lower than the right for PD subjects ($p < 0.02$) but not in healthy controls. Both PD and normal subjects had significantly higher ADC at the left SN compared to the right SN ($p < 0.03$). Further analyses showed a significant Group by ROI interaction for FA at the right rostral SN ($p < 0.02$), and ADC at the left rostral SN ($p < 0.02$). Only the rostral SN showed significant asymmetry in FA and ADC, and amongst PD subjects only. Table 2 shows the mean FA and ADC at the rostral SN of PD and normal subjects.

PD subjects had significantly lower FA ($p < 0.005$) and significantly higher ADC ($p < 0.00005$) at the left rostral SN compared to the right. Normal subjects showed similar but non significant trends. The differences across the left and right rostral SN were significantly different between PD and normal subjects for FA ($p < 0.05$) and ADC ($p < 0.02$). At the left rostral SN, PD subjects had a significantly higher ADC than healthy controls ($p < 0.01$). The FA at the rostral SN was significantly lower than the FA at the ipsilateral cerebral peduncle for PD subjects (right side: $t = 13.0$, $p < 0.0000002$; left side: $t = 10.2$, $p < 0.000002$). Similar observations were noted in normal subjects (right side: $t = 11.4$, $p < 0.0000002$; left side: $t = 12.5$, $p < 0.0000001$).

We did not find any significant difference in DTI indices between the contralateral and ipsilateral SN in PD subjects, with reference to the clinically most affected side. Further analyses showed all five PD subjects with clinically affected side on the right, and the single PD subject with bilateral clinical involvement, had lower FA at the left rostral SN compared to the right. On the other hand, only one out of the five PD subjects with clinically affected side on the left had lower FA at the right rostral SN compared to the left. All PD subjects had higher ADC at the left rostral SN compared to the right.

3.2. Correlations between DTI indices and motor severity

Correlation analyses between the DTI indices and the various factors such as age, disease duration and disease severity were performed. There was a significant positive correlation between the UDPRS motor score and FA ($r = 0.7$, $p < 0.03$), observed only at the left rostral SN. There were no significant correlations between the DTI indices with age or disease duration. Using the left cerebral peduncle/left rostral SN ratio as an index, a significant negative correlation was noted between the UPDRS motor score and this FA index ($r = -0.7$, $p < 0.03$). Further analyses showed a U-shape relationship between FA and disease severity at the left rostral SN, with minimal variation of FA values at the right rostral SN across

Table 1
Mean FA and ADC at the SN for PD and normal subjects.

	PD		*p*-value	Normal		*p*-value
	Right SN	Left SN		Right SN	Left SN	
FA (mean ± standard deviation)	0.451 ± 0.043	0.406 ± 0.041	<0.02	0.430 ± 0.025	0.439 ± 0.043	NS
ADC (mean ± standard deviation)	0.00232 ± 0.000195	0.00250 ± 0.000148	<0.03	0.00230 ± 0.000132	0.00239 ± 0.000127	<0.03