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Utility of manual fractional anisotropy measurements in the management of patients with Parkinson disease: a feasibility study with a 1.5-T magnetic resonance imaging system

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Abstract

Background: Diffusion tensor imaging has emerged as a promising tool for quantitative analysis of neuronal damage in Parkinson disease, with potential value for diagnostic and prognostic evaluation.

Purpose: The aim of this study was to examine Parkinson disease-associated alterations in specific brain regions revealed by diffusion tensor imaging and how such alterations correlate with clinical variables.

Material and Methods: Diffusion tensor imaging was performed on 42 Parkinson disease patients and 20 healthy controls with a 1.5-T scanner. Manual fractional anisotropy measurements were performed for the ventral, intermediate, and dorsal portions of the substantia nigra, as well as for the cerebral peduncles, putamen, thalamus, and supplementary motor area. The correlation analysis between these measurements and the clinical variables was performed using χ^2 variance and multiple linear regression.

Results: Compared to healthy controls, Parkinson disease patients had significantly reduced fractional anisotropy values in the substantia nigra ($P < .05$). Some fractional anisotropy measurements in the substantia nigra correlated inversely with duration of Parkinson disease and Parkinson disease severity scores. Reduced fractional anisotropy values in the substantia nigra were also correlated inversely with age variable. fractional anisotropy values obtained for the right and left putamen varied significantly between males and females in both groups.

Conclusion: Manual fractional anisotropy measurements in the substantia nigra were confirmed to be feasible with a 1.5-T scanner. Diffusion tensor imaging data can be used as a reliable biomarker of Parkinson disease that can be used to support diagnosis, prognosis, and progression/treatment monitoring.

Keywords

Parkinson disease, substantia nigra, magnetic resonance imaging, diffusion tensor imaging, biomarker

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Introduction

Parkinson disease (PD) is characterized by a progressive loss of dopaminergic neurons in the pars compacta region of the substantia nigra (SN) and α-synuclein aggregate accumulation in the brain stem, spinal cord, and cortex.[1] Although PD diagnosis is based primarily on clinical findings, magnetic resonance imaging (MRI) studies provide important information for differential diagnosis, including ruling out atypical parkinsonism and structural lesions.

The development of advanced MRI techniques, including proton magnetic resonance spectroscopy,

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diffusion tensor imaging (DTI), and functional MRI, has augmented the utility of MRI in the early diagnosis of PD.[2] These advanced techniques yield measurements that can be correlated with disease severity scales, making them potentially useful for staging and management.[3] In recent years, DTI has emerged as a promising tool for identifying and quantitating localized microstructural changes in sites where conventional MRI does not reveal significant alterations. Additionally, DTI provides a unique window into assessing changes in neuronal connectivity and allows quantitative measurements of the integrity of brain nuclei and white matter tracts.

Water diffusibility reductions in the SN of patients with PD have been reported to correlate inversely with disease severity, with mild reductions being evident even in early-stage PD.[4–10] In a systematic review and meta-analysis, Cochrane et al.[11] found significant fractional anisotropy (FA) reductions in patients with PD. Conversely, in their meta-analysis, Schwarz et al.[12] did not find a consistent reduction in FA within the SN. This inconsistency was attributed to variability among the studies, including inter-study differences in cohort characteristics, scanner magnetic fields, and DTI sequence parameters.

Although changes in diffusibility have also been observed in the striatum, thalamus, olfactory bulbs, frontal lobes, and cerebellar hemispheres of patients with PD,[6,13–16] relevant systematic reviews and meta-analyses have generated conflicting results.[17–19] Consequently, clinicians do not yet have reliable DTI markers of PD, particularly for identifying early-stage PD and assessing PD progression. The aim of the present study was to test the hypothesis that it is feasible to establish PD biomarkers with manual FA measurements within specified brain regions using scanners that are ubiquitously available.

Material and Methods

Subjects

We enrolled 42 patients with a diagnosis of idiopathic PD based on the UK PD Society Brain Bank's diagnostic criteria[20] as well as 20 healthy controls (HCs) with no MRI abnormalities and no history of neurological or psychiatric disease. The patients were seen at the ambulatory clinic for movement disorders at our institution and then referred for clinical and imaging examination, regardless of sex, age, disease duration, or medication use. All 42 patients were taking antiparkinsonian drugs. The exclusionary criteria were structural brain lesions, atypical parkinsonism, a Mini-Mental State Exam score $\leq$24, or any MRI contraindication. Written informed consent was obtained from each participant in accordance with the Declaration of Helsinki. Our institutional review board approved this study.

Clinical evaluation

A neurologist (JSP) with more than 30 years of experience in movement disorders conducted the clinical evaluations and determined PD severity with the Unified Idiopathic Parkinson Disease Rating Scale (UPDRS III)[21] and Hoehn & Yahr staging. The demographic and clinical characteristics of the PD patients and HCs are summarized in Table 1.

MRI acquisition

MRI was performed with a 1.5-T scanner (Optima 360 Advance, General Electric Healthcare, Waukesha, WI). The examination protocols included: a sagittal three-dimensional T1-weighted fast spoiled gradient echo inversion recovery sequence (repetition time (TR) = 8.964 ms, echo time (TE) = 3.796 ms, inversion time (TI) = 500 ms, flip angle = 8°, section thickness = 1 mm, field of view (FOV) = 240 mm, matrix size = 256 × 256,

Table 1. Summary of and inter-group comparisons of study participant characteristics.

Characteristic	HCs	PD patients	Total	*P*
N	20 (32%)	42 (68%)	62	
SEX				.004*
Female	15 (75%)	15 (36%)	30	
Male	5 (25%)	27 (64%)	32	
Mean age, years	58.20 ± 6.06	65.9 ± 9.64		.002*
Mean MMSE score	27.55 ± 1.23	25.86 ± 2.94		>.050
Mean disease duration, months	–	79.62 ± 43.26		
Mean Hoehn & Yahr scale score	–	2.39 ± 0.67		
Mean UPDRS III score	–	25.9 ± 10.15		

Note: Means are reported with ± standard deviations.
*$P < .05$.

number of excitations (NEX) = 0, 8); an axial T2-weighted FLAIR sequence with fat suppression (TR = 11,000 ms, TE = 87.12 ms, TI = 2,700 ms, flip angle = 90°, section thickness = 5 mm, FOV = 240 mm, matrix size = 256 × 190, NEX = 1); and an axial enhanced three-dimensional multi-echo gradient-echo T2*-weighted angiography (ESWAN) sequence (TR = 75.6 ms, TE = 48.07 ms, flip angle = 20°, section thickness = 2.4 mm, FOV = 240 mm, matrix size = 256 × 256, NEX = 0.686719). For DTI, an isotropic diffusion-weighted spin-echo echo-planar imaging sequence (TR = 8,445 ms, TE = 88.5 ms, section thickness = 2.4 mm, FOV = 240 mm, matrix size = 100 × 100, NEX = 1, number of T2-weighted acquisitions = 4) was applied on an axial plane with diffusion-sensitizing gradients along 26 directions (b-value of 0 and 1000 s/mm^2). The total imaging examination time was about 17 min.

Image processing and analysis

For image postprocessing, mean diffusivity and FA maps were developed from DTI data after automated segmentation of brain from nonbrain tissues and correction of eddy currents in Advantage Workstation 4.6 (General Electric Healthcare, Waukesha, WI). A neuroradiologist (RVO) with more than 10 years of experience, who was blinded to the clinical data, conducted visual evaluation of the images in Osirix Imaging Software Advance Open-Source PACS Workstation DICOM Viewer v.4.1.1 32-bit (Pixmeo, Sarl, Geneva, Switzerland). Subsequently, manual image analysis was used to define three circular regions of interest (ROIs), each with an area of 0.125 cm^2, including one in the SN of each hemisphere, identified as a dark band on a trace map, as well as one in the cerebral peduncle (Fig. 1(a)). These ROIs were copied and pasted onto FA maps (Fig. 1(b)). Free-hand defined ROIs were drawn around both putaminal nuclei in the ESWAN sequences (Fig. 1(c)), and then also copied and pasted onto FA maps (Fig. 1(d)). Oval ROIs (1.0 cm^2 area) were placed over each side of the thalamus on FA maps (Fig. 1(e)). Circular ROIs (0.5 cm^2 area) were placed in the subcortical white matter of the supplementary motor area (SMA) on FA maps (Fig. 1(f)), guided by the parasagittal gyrus bounded posteriorly by primary motor cortex.

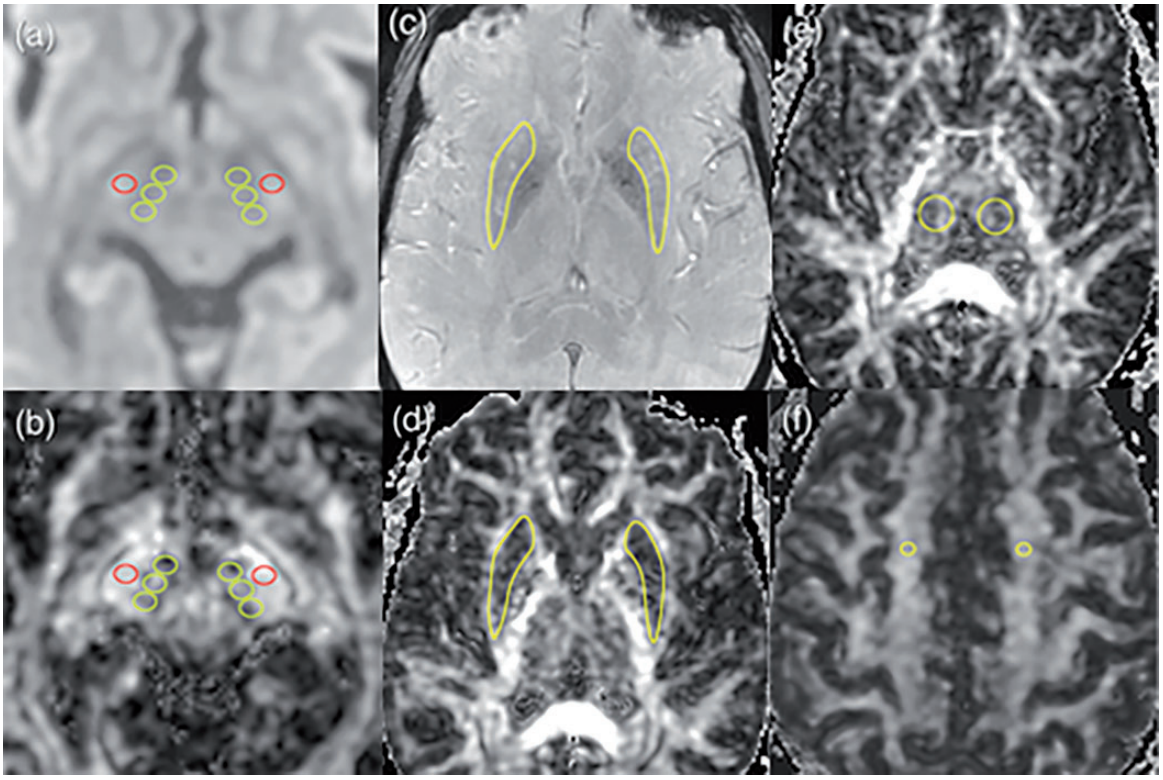

Fig. 1. Mesencephalon measurements: white circles indicate the substantia nigra (SN) and black circles indicate the cerebral peduncles in mean diffusivity (a) and fractional anisotropy (FA) (b) maps. Putamen measurements: white lines indicate the putamen in ESWAN (c) and FA (d) maps. Thalamus and supplementary motor area (SMA) measurements: white circles indicate measurements in both thalami (e) and black circles indicate SMAs (f) in FA maps.

Statistical analysis

Based on an infinite population (>10,000) and the national prevalence of PD, we calculated a sample size of 49.[22] The Kolmogorov–Smirnov test was applied to evaluate data distributions. We used χ^2 tests for inter-group comparisons of demographic variables and inter-group inferential analyses of clinical variables (parametric data) and used Mann–Whitney U tests for comparisons of variables with non-parametric data. We conducted linear regression analyses to assess the relationships of measured variables with FA measurements. The measures that achieved significance were submitted to a multiple linear regression adjusted for age and sex. The criterion of statistical significance used was $P < .05$. β values are reported with 95% confidence intervals (CIs). The analysis was performed by the software SPSS Statistics, version 20.0.0 (IBM, Armonk, NY, USA).

Results

Group characteristics

Compared to the HC group, the PD patient group had a significantly higher mean age and a significantly greater proportion of males (Table 1).

Conventional MRI

Age-related white matter changes were detected in 18/20 HCs (90%) and 38/42 PD patients (90.48%). Applying Fazekas scale,[23] 15 HCs had mild changes (75%) and 2 HCs had moderate changes (10%), while 29 PD patients had mild changes (69.05%), 7 PD patients had moderate changes (16.67%), and 2 PD patients had severe changes (4.76%). No other notable changes were found in these sequences in either group.

Factors that affect and correlate with FA in ROIs

Compared to HCs, we observed significantly altered mean FA measurements for the PD patient group in the intermediate and dorsal portions of the right SN, as well as in the average of the three measurements in both the right SN and the left SN (Table 2). Age was a significant factor for FA measurements in the intermediate and dorsal portions of the right SN, averaged FA across the three measurements in the right SN, FA in the intermediate portion of the left SN, averaged FA across the three measurements in the left SN, and FA values in the right and left SMA. FA values obtained for the right and left putamen varied significantly between males and females in both groups (Table 3).

Among patients with PD, we found that disease duration had a significant correlative relationship

Table 2. Comparisons of mean FA measurements between HC and PD groups.

Region	HC	PD	*P*	*B*	95% CI
Right SN					
Ventral	0.450	0.442	.666	−0.008	(−0.044 to 0.028)
Middle	0.515	0.449	<.001*	−0.065	(−0.098 to −0.033)
Dorsal	0.486	0.428	.002*	−0.058	(−0.094 to −0.022)
Average	0.484	0.440	.001*	−0.044	(−0.068 to −0.019)
Left SN					
Ventral	0.465	0.436	.177	−0.030	(−0.73 to 0.140)
Middle	0.475	0.445	.100	−0.031	(−0.067 to 0.006)
Dorsal	0.445	0.409	.053	−0.036	(−0.072 to 0.001)
Average	0.462	0.429	.020*	−0.033	(−0.610 to −0.005)
Cerebral peduncle					
Right	0.768	0.778	.471	0.009	(−0.017 to 0.036)
Left	0.785	0.769	.291	−0.016	(−0.047 to 0.014)
Thalamus					
Right	0.319	0.315	.738	−0.004	(−0.027 to 0.019)
Left	0.312	0.310	.819	−0.002	(−0.019 to 0.015)
Putamen					
Right	0.246	0.249	.784	0.003	(−0.017 to 0.022)
Left	0.229	0.238	.406	0.008	(−0.011 to 0.026)
Frontal areas					
Right	0.620	0.608	.625	−0.011	(−0.058 to 0.035)
Left	0.614	0.602	.540	−0.012	(−0.050 to 0.027)

*$P < .05$.

with FA measurements in the intermediate and dorsal portions of the right SN as well as with mean FA values for the three SN regions (Table 4). Additionally, among patients with PD, Hoehn & Yahr scale severity scores correlated significantly with FA values in the intermediate and dorsal portions of the right SN, as well as with the average of the three measurements within the right SN. Similarly, Hoehn & Yahr scale severity scores correlated significantly with FA measurements in the intermediate portion of the left SN as well as with the average of the three FA measurements in the left SN (Table 4). UPDRS III scores correlated significantly with FA measurements in the intermediate portion of the right SN as well as with the average of the three FA measurements in the left SN (Table 4).

Table 3. Analysis of sex and age effects on FA measurements in both groups.

	Sex		Age	
FA region	*P*	*B*	*P*	β
Right SN				
Ventral	.775	0.285	.546	0.001
Middle	.191	−1.262	.011*	−0.002
Dorsal	.660	0.407	.016*	−0.002
Average	.798	−0.342	.042*	−0.001
Left SN				
Ventral	.221	0.983	.197	−0.001
Middle	.639	−0.449	.040*	−0.002
Dorsal	.641	0.444	.172	−0.001
Average	.478	0.878	.021*	−0.002
Cerebral peduncle				
Right	.841	0.274	.375	0.001
Left	.844	−0.225	.589	<0.001
Thalamus				
Right	.413	1.280	.904	<0.001
Left	.984	0.043	.677	<0.001
Putamen				
Right	<.001*	6.967	.289	0.001
Left	<.001*	7.063	.515	<0.001
Frontal areas				
Right	.159	1.107	.004*	−0.003
Left	.603	0.057	<.001*	−0.003

*$P < .05$.

Discussion

In the present study, significantly reduced FA values were found in PD patients, compared to HCs. Additionally, we found that some FA measurements in the SN of PD patients correlated inversely with duration of PD and PD severity. Both sex and age had significant effects on FA measurements in ROIs.

It is well established that aging leads to changes in the function, structure, and physiology of the human brain.[24] Our finding of a greater prevalence of age-related grade 2/3 white matter changes in the PD patient group, compared to HCs, can be attributed to the older age profile of the PD patient group.[23] Some FA measurements in the SN were related significantly to age, corroborating the findings of Vaillancourt et al.[24] and a post-mortem study by Jyothi et al.[25] We also observed an effect of age on FA in the SMA, consistent with prior pathology and DTI studies showing a relationship between aging and neurodegeneration.[26,27]

We demonstrated a highly significant effect of sex on FA measurements in the putamen, even after adjusting for disease duration and age. Neuroanatomical differences between the sexes may explain observed differences in behavioral and cognitive measures.[28] In a recent meta-analysis of eight DTI studies of gray matter that used automated voxel-based analyses, Ruigrok et al.[29] found that men had greater neuronal density in the putamen than women, but did not

Table 4. Correlation of FA measurements with clinical variables in PD patients.

	Disease duration		Hoehn & Yahr		UPDRS III	
FA region	*P*	β	*P*	*B*	*P*	β
Right SN						
Ventral	.172	−0.013	.387	−0.007	.577	0.004
Middle	.001*	−0.030	.006*	−0.020	.013*	−0.018
Dorsal	.028*	−0.021	.011*	−0.020	.076	−0.014
Average	.001*	−0.021	.004*	−0.016	.097	−0.009
Left SN						
Ventral	.201	−0.015	.051	−0.018	.326	−0.009
Middle	.652	−0.004	.044*	−0.016	.100	−0.012
Dorsal	.203	−0.012	.112	−0.013	.050	−0.015
Average	.173	−0.010	.009*	−0.015	.041*	−0.012

*$P < 0.05$.

identify sex differences in manual FA measurements of the putamen in the reviewed literature.

The presently observed trend of more PD-associated FA alterations in the left hemisphere than in the right fits with Knossalla et al.'s[10] description of asymmetric SN involvement in PD. This asymmetry may underlie the lateralization of symptoms experienced by patients with PD, pointing to a new area of DTI exploration in PD research.

Group differences in FA were more pronounced in the posterior SN than in the anterior SN, consistent with Vaillancourt et al.'s[7] prior demonstration of a highly reproducible, 100% accurate distinction between these areas. Differences between FA measurements in the ventral SN and dorsal SN can be explained by a greater loss of dopaminergic cells in the latter, as demonstrated in a previous postmortem study.[30] Indeed, nigrossome-1—a cluster of dopaminergic cells that is particularly susceptible to PD degeneration—is located in the dorso-lateral SN. Nigrossome-1 cannot be readily delineated in patients with PD using 3-T susceptibility-weighted imaging due to iron overload.[31] Consistent with the present findings, this preferential degeneration of the dorsal SN has also been demonstrated in studies that quantified iron overload and neuromelanin by MRI.[32,33]

Importantly, we found that FA in the SN correlates inversely with PD severity (Fig. 2) and duration (Fig. 3), though the only prior examination of this correlation in the literature, to our knowledge, did not demonstrate statistically significant correlations.[5] Of three prior studies employing manual methods examining potential SN FA correlations with Hoehn & Yahr scale scores, two studies demonstrated significant correlations,[3,4,34] consistent with the present results, and one failed to demonstrate such as correlation.[3]

Automated voxel-based analyses produce findings similar to findings obtained with manual measures,[35] including significant FA reductions in the SN in patients with PD.[6,13] Using both manual and automated FA analyses, Zhan et al.[13] showed an inverse correlation of SN measurements with UPDRS III scores. Using only a manual method, Modrego et al.[3] demonstrated an inverse correlation between these variables. However, Du et al.[5] did not obtain a significant SN FA correlation with UPDRS III scores, probably due to their small number of patients with PD and limited spectrum of scale scores.

With respect to negative findings in the present study, we did not observe significantly reduced FA in the frontal lobes, putamen, thalamus, or cerebral peduncles in patients with PD. However, a number of prior studies have reported reduced frontal lobe FA in PD and attributed the reduction to degeneration in the premotor cortex and SMA.[8,9,13,26] FA changes in these regions have been demonstrated even in early-stage PD, prior to clinically significant cortical atrophy.[9] The age difference between our PD and HC groups may explain, at least in part, our lack of a significant frontal lobe FA reduction in our PD patient group. Previously reported DTI changes in the putamen of patients with PD have been thought to be attributable to dopaminergic nigrostriatal projection loss.[6] Our negative findings in the putamen, however, are consistent with other studies that conducted manual analyses.[4,8] Reductions in FA in the thalamus have been demonstrated in patients with PD, both with manual and automated methods, and this finding has been related to disease severity as well as to dementia and depression.[36] Notwithstanding, our negative finding for the thalamus is in agreement with two prior DTI studies.[4] Finally, our not finding FA reductions in the cerebral peduncles of our PD patients is consistent with prior studies; indeed, the peduncles have been used as a reference region to enable distinction of the SN.[3,7,10]

Reduced FA in the SN can be explained by the degeneration of dopaminergic neurons, especially in

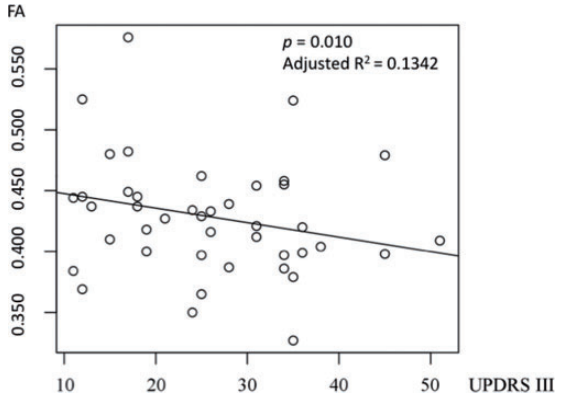

Fig. 2. Distribution of mean FA values obtained for the left SN in relation to UPDRS III scores.

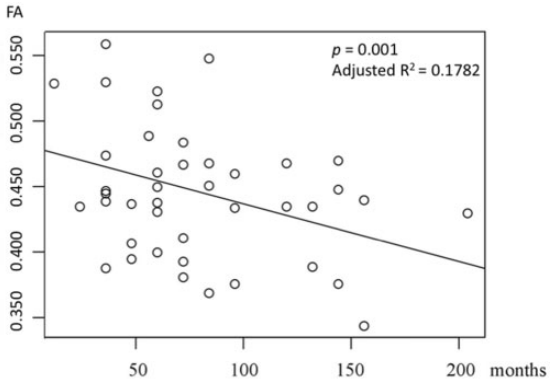

Fig. 3. Distribution of mean FA values obtained for the right SN in relation to PD duration.

the dorsal SN. The presently observed group differences in SN FA measurements corroborate the findings of seven prior studies that employed manual measurements of FA in the SN.[4,5,7,8,10,13] However, only two of these seven prior studies were performed with a 1.5-T MRI scanner.[4,8] The others used 3-T MRI scanners or advanced voxel-based automated methods, which are not readily translatable to clinical application. Importantly, our demonstrations of SN FA reductions correlating inversely with PD duration and severity support the notion that DTI conducted with a 1.5-T MRI scanner can be used to identify PD biomarkers that may be useful for PD diagnosis, prognosis, and therapy management.

This study has some limitations. First, the lack of gold-standard histopathological diagnoses of PD could lead to diagnostic bias. Secondly, FA values were obtained manually, which could have introduced a measurement bias. Thirdly, free-hand ROI delineation of putaminal nuclei could affect reproducibility and lead to measurement bias. Fourthly, reproducibility could not be assessed because all image analyses were performed by only one observer. Finally, because symptom laterality was not assessed, we could not analyze the potential relationship between FA asymmetry of symptom asymmetry.

In conclusion, this study demonstrated that PD-related changes in FA can be demonstrated by DTI with a 1.5-T scanner, which allows for examination times that are feasible in clinical practice. Larger sample studies are needed for protocol optimization and standardization, to further validate the present findings, and to evaluate the utility of combining DTI with novel methods, such as iron overload and neuromelanin quantitation methods.

Declaration of Conflicting Interests

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