Ann Med Res 2021;28(6):1223-7

Annals of Medical Research

DOI: 10.5455/annalsmedres.2020.12.1227

Original Article

Diffusion tensor imaging findings of patients with parkinson's disease refractory to medical treatment

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Abstract

Aim: Diffusion Tensor Imaging (DTI) findings can be useful to detect and measure neurodegeneration that is seen in Parkinson's disease (PD). Microstructural changes in regions of the brain related with motor function are evaluated by using DTI measurements of fractional anisotropy (FA) to find out the possible role of the technique in diagnosis in patients with PD.

Materials and Methods: The study includes 18 PD patients who were candidates for deep brain stimulation surgery, and 19 control group patients. DTI was performed in all cases. DTI characteristics of FA were measured in primary motor cortex (M1), supplementary motor area (SMA), inferior parietal lobule, putamen (P), globus pallidus externus (GPe) and internus (GPi), ventrolateral nucleus of thalamus (Th), substantia nigra (SN), cuneus, precuneus and cerebellar dentate nucleus (D) bilaterally. Additionally, we processed "raw" FA images and colored them according to fiber orientation to visualize STN and GPi nuclei.

Results: Mean age of the control group was 59.2±13.2 (range: 31-79) years, while it was 56.7±16 (range: 42-77) years for the patient group. Mean duration of PD was 12.4±7.1 (range: 5-30) years. Study group FA values were significantly lower than the control group in all areas bilaterally ($p<0.05$). Additionally, FA-M1, FA-GPi and FA-GPe values were significantly lower on left side compared to right side ($p<0.05$).

Conclusion: Decrease in FA values in all regions in the study group is thought to result from loss of nerve cells. Additionally, raw FA images that are processed, and colored in relation to fiber orientation can be useful for a better identification of STN and GPi nuclei. This type of imaging will provide a more precise anatomy necessary for surgical targeting.

Keywords: Diffusion tensor imaging; neurodegenerative diseases; parkinson disease

INTRODUCTION

Parkinson's Disease (PD) is the second most common neurodegenerative disease following Alzheimer's disease. It is still not known what triggers the progressive and selective neuronal dysfunction and loss in the disease (1).

Mostly, at the time of clinical diagnosis, 60-70% of dopaminergic neurons are already degenerated. When the diagnosis is late, the treatments usually fail to keep progression of the disease, therefore early diagnosis, objective measurements of the disease progression, and treatment modalities that can modify the disease progression are important (2).

Previous studies analyzed biomarkers for PD and techniques to measure amount and extent of pathologic processes. Emission tomography (SPECT or PET) used in the diagnosis is an expensive modality that has limited availability requiring radioactive tracers (3–8). Magnetic resonance (MR) imaging is a useful technique in differentiation of Parkinson syndromes, facilitating early diagnosis and, follow-up of disease progression.

Diffusion tensor imaging (DTI) is an in vivo MR-tractography technique that evaluates orientation and integrity of the brain's white mater tracts, enabling measurement of microstructural changes or differences indirectly. This is provided by analyzing the degree of displacement of water molecules, in terms of fractional anisotropy (FA) (1,2,9-11). Diffusion tensor imaging can detect tissue alterations in the early phase of PD (1,2).

The purpose of this study is to analyze the ability of DTI to identify microstructural changes inside the brain tissue related to motor function in PD.

Received: 03.01.2021 **Accepted:** 04.03.2021 **Available online:** 24.06.2021
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MATERIALS and METHODS

Eighteen patients (6 female and 12 male) with a minimum of 2 of 3 cardinal signs and an established previous response to dopaminergic treatment were enrolled to the study. Dopaminergic drugs were discontinued 12 hours before analysis to prevent interactions resulting from their effects on basal ganglia. The average duration of treatment of patients was 10 years and Hoehn&Yahr (H&Y) grade was 2.1. Control group included 19 patients (12 female and 7 male) who had cranial MR imaging for different reasons. Control patients with neurologic (trauma, epilepsy, stroke, etc.), psychiatric or systemic diseases involving brain were excluded from the study.

Written informed consent was obtained before MR imaging from all participants. The study was approved by the Okan University, School of Medicine, Ethical Review Board (Study no; 11-2019-115) and conducted in accordance with the declaration of Helsinki.

Diffusion Tensor Imaging characteristics of FA were measured in primary motor cortex (M1), supplementary motor area (SMA), inferior parietal lobule, putamen (P), globus pallidus externus (GPe) and internus (GPi), ventrolateral nucleus of thalamus (Th), substantia nigra (SN), cuneus, precuneus and cerebellar dentate nucleus (D) bilaterally. Additionally, "raw" FA images were processed and colored according to fiber orientation to visualize STN and GPi nuclei. Analysis of DTI and processing of FA images were done by a team of six radiologists which included one dedicated neuroradiologist.

The MR imaging system (GE Healthcare, Milwaukee, WI, USA) was operated at 1.5 T using 8 channeled standard head coil. Imaging protocol was as follows: Axial plane, 3D T2 (TR: 4700, TE: 85) and 3D PD (TR: 3400, TE: 13), slice thickness 2 mm, spacing: 0, matrix: 256x256, FOV: 24 cm and NEX: 2. DTI; 12 direction (TR: 8000, TE: min), slice thickness 5 mm, spacing:1, matrix: 128x128, FOV:26 cm.

Statistical Analyses

Descriptive statistics calculations including mean, standard deviation, median, lowest, highest, frequency and percentage values were used to analyze the data. The distribution of the variables was tested by Kolmogorov-Smirnov test, and found normal distribution. Mann–Whitney U test was used to compare distribution of age, and FA values, and chi-square test was performed for comparing distribution of qualitative-independent data (gender, and presence or absence of dementia). A value of $p<0.05$ was considered as statistically significant. SPSS, Version 26.0 (IBM Corp., Armonk, N.Y.) was used for the statistical analyses.

RESULTS

Parkinson's disease group and control group mean age were 56.7±16 (range:42-77) years and 59.2±13.2 (31-79) years, respectively. The average duration of disease was 12.4±7.1 (range:5-30) years. There was no statistically significant difference between 2 groups with respect to age (p=0.819) (Table 1).

Table 1. Distribution of age, sex, and presence of memory deficit in Parkinson's disease and control group

	PD group			Control group			p	
	Mean±SD		Median	Mean±SD		Median		
Age	56.7 ± 16.0		60.5	59.2 ± 13.2		60.0	>0.05	m
	n	% (N=21)		n	% (N=21)			
Gender								
Female	6	28.6%		12	63.2%		>0.05	X^2
Male	15	71.4%		7	36.8%			
Dementia								
(-)	21	100.0%		19	100.0%		>0.05	X^2
(+)	0	0.0%		0	0.0%			

m: Mann-Whitney U test, PD: Parkinson's disease, SD: Standard Deviation, X^2: Chi-square test

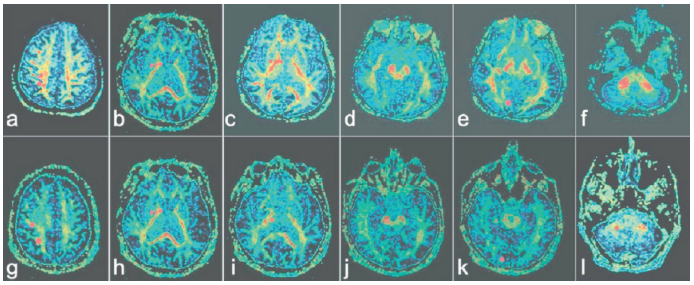

Figure 1. Axial sections of colored fractional anisotropy map of SMA (anterior red dot) and M1 (posterior red dot) (a), GPi, GPe, putamen (from medial to lateral respectively) (b), Th (c), SN (d), cuneus (e), and cerebellar dentate nucleus (f) in a normal person (control group), and a patient with PD (g) (h) (i) (j) (k) (l), respectively. The decrease in the intensity of signals is seen in the PD patient. (red dots are added for signing the localization on the right cerebral hemisphere) (GPe: globus pallidus externus, GPi: globus pallidus internus, M1: primary motor cortex, PD: Parkinson's disease, SMA supplementary motor area, SN: substantia nigra, Th: ventrolateral nucleus of thalamus)

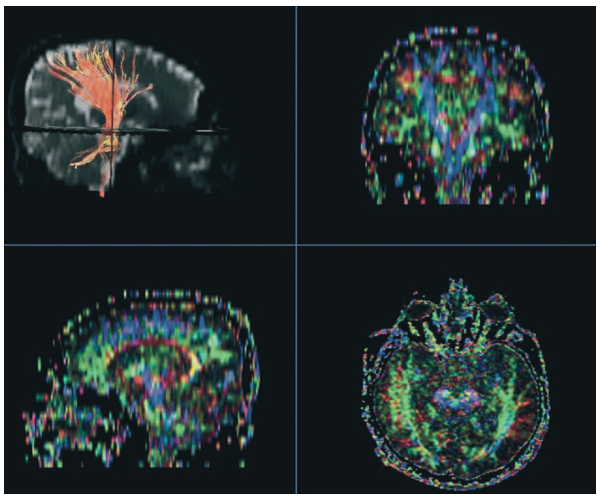

Figure 2. Fiber tractography of a PD patient (upper left), processed from colored DTI in axial (lower right), coronal (upper right), and sagittal (lower left) sections. These images can be superposed on related cerebral structures and processed in any projection three dimensionally

Table 2. Fractional anisotropy values on the right side in Parkinson's disease and control group

	PD Group		Control Group		p-value	
	Mean±SD	Median	Mean±SD	Median		
R-FA-M1	0.23 ± 0.09	0.16	0.31 ± 0.08	0.31	**<0.001**	m
R-FA-SMA	0.25 ± 0.09	0.12	0.36 ± 0.08	0.39	**<0.001**	m
R-FA-Parietal	0.17 ± 0.05	0.12	0.32 ± 0.07	0.33	**<0.001**	m
R-FA-GPi	0.09 ± 0.01	0.08	0.44 ± 0.10	0.47	**<0.001**	m
R-FA-GPe	0.07 ± 0.01	0.07	0.31 ± 0.07	0.31	**<0.001**	m
R-FA-P	0.08 ± 0.02	0.08	0.29 ± 0.05	0.30	**<0.001**	m
R-FA-precuneus	0.08 ± 0.01	0.08	0.34 ± 0.07	0.32	**<0.001**	m
R-FA-Cuneus	0.08 ± 0.01	0.08	0.35 ± 0.07	0.34	**<0.001**	m
R-FA-Th	0.08 ± 0.01	0.08	0.56 ± 0.13	0.58	**<0.001**	m
R-FA-SN	0.08 ± 0.01	0.08	0.54 ± 0.08	0.54	**<0.001**	m
R-FA-D	0.07 ± 0.01	0.07	0.64 ± 0.07	0.62	**<0.001**	m

D: Dentate Nucleus, FA: Fractional Anisotropy, GPe: Globus Pallidus Externus, GPi: Globus Pallidus Internus, m: Mann-Whitney U test, M1: Primary Motor Cortex, P: Putamen, PD: Parkinson's Disease, R: right, SD: Standard Deviation, SMA: Supplementary Motor Area, SN: Substantia Nigra, Th: Ventrolateral Nucleus of Thalamus

Table 3. Fractional anisotropy values on the left side in Parkinson's disease and control group

	PD Group		Control Group		p-value	
	Mean±SD	Median	Mean±SD	Median		
L-FA-M1	0.15 ± 0.04	0.14	0.34 ± 0.08	0.34	**<0.001**	m
L-FA-SMA	0.12 ± 0.03	0.12	0.37 ± 0.07	0.35	**<0.001**	m
L-FA-Parietal	0.12 ± 0.02	0.11	0.33 ± 0.07	0.33	**<0.001**	m
L-FA-GPi	0.08 ± 0.01	0.08	0.40 ± 0.07	0.41	**<0.001**	m
L-FA-GPe	0.06 ± 0.01	0.07	0.28 ± 0.06	0.26	**<0.001**	m
L-FA-P	0.08 ± 0.01	0.08	0.28 ± 0.05	0.28	**<0.001**	m
L-FA-Precuneus	0.08 ± 0.01	0.08	0.35 ± 0.08	0.32	**<0.001**	m
L-FA-Cuneus	0.08 ± 0.01	0.08	0.35 ± 0.07	0.35	**<0.001**	m
L-FA-Th	0.08 ± 0.01	0.08	0.56 ± 0.14	0.58	**<0.001**	m
L-FA-SN	0.09 ± 0.01	0.09	0.54 ± 0.14	0.53	**<0.001**	m
L-FA-D	0.07 ± 0.01	0.07	0.65 ± 0.07	0.65	**<0.001**	m

D: Dentate Nucleus, FA: Fractional Anisotropy, GPe: Globus Pallidus Externus, GPi: Globus Pallidus Internus, L: Left, m: Mann-Whitney U test, M1: Primary Motor Cortex, P: Putamen, PD: Parkinson's Disease, SD: Standard Deviation, SMA: Supplementary Motor Area, SN: Substantia Nigra, Th= Ventrolateral Nucleus of Thalamus

Table 4. Comparison of fractional anisotropy values on the left and right sides in Parkinson's disease group

	Right		Left		p-value	
	Mean±SD	Median	Mean±SD	Median		
FA-M1	0.23 ± 0.09	0.16	0.15 ± 0.04	0.14	**<0.05**	m
FA-SMA	0.25 ± 0.09	0.12	0.12 ± 0.03	0.12	>0.05	m
FA-Parietal	0.17 ± 0.05	0.12	0.12 ± 0.02	0.11	>0.05	m
FA-GPi	0.09 ± 0.01	0.08	0.08 ± 0.01	0.08	**<0.05**	m
FA-GPe	0.07 ± 0.01	0.07	0.06 ± 0.01	0.07	**<0.05**	m
FA-P	0.08 ± 0.02	0.08	0.08 ± 0.01	0.08	>0.05	m
FA-Precuneus	0.08 ± 0.01	0.08	0.08 ± 0.01	0.08	>0.05	m
FA-Cuneus	0.08 ± 0.01	0.08	0.08 ± 0.01	0.08	>0.05	m
FA-Th	0.08 ± 0.01	0.08	0.08 ± 0.01	0.08	>0.05	m
FA-SN	0.08 ± 0.01	0.08	0.09 ± 0.01	0.09	>0.05	m
FA-D	0.07 ± 0.01	0.07	0.07 ± 0.01	0.07	>0.05	m

D: Dentate Nucleus, FA: Fractional Anisotropy, GPe: Globus Pallidus Externus, GPi: Globus Pallidus Internus, m: Mann-Whitney U test, M1: Primary Motor Cortex, P: Putamen, PD: Parkinson's Disease, SD: Standard Deviation, SMA: Supplementary Motor Area, SN: Substantia Nigra, Th= Ventrolateral Nucleus of Thalamus

Parkinson's disease group showed significantly lower FA-M1, FA-SMA, FA-Parietal, FA-GPi, FA-GPe, FA-P, FA-Precuneus, FA-Cuneus, FA-Th, FA-SN and FA-D values compared to control group on the right side ($p<0.001$) (Table 2), and the left side (Table 3) ($p<0.001$). Additionally, left side FA-M1, FA-GPi and FA-GPe values were significantly lower than the right side in the patient study group (Table 4). Other measurements in the PD group did not show significant differences between left and right side ($p>0.05$).

Colored fractional anisotropy map of a normal person and a person with PD is shown in Figure 1. Processed and colored DTI map of these is presented respectively in Figure 2.

DISCUSSION

Understanding the mechanism of pathogenesis is an important target of PD researchers, to know the clinical follow-up and develop treatment strategies (12). There are studies about etiopathogenesis of PD, done by using PET and SPECT (3–8). PET, and SPECT are not sensitive enough to differentiate putamen from globus pallidus, or lateral and medial globus pallidus from each other anatomically, therefore inconsistent results are reported about the role of these structures in PD pathogenesis (3). Dopaminergic cell loss is not the sole problem in PD. Diffusion tensor imaging measures dopamine function and activity in the nerve terminals, more than cell count, and this makes it a promising modality for early diagnosis (8).

Studies have shown that, diffusion changes can be seen before the appearance of atrophy or signal changes in the standard MR imaging sequences, therefore use of DTI to analyze the diffusion changes in PD is rational (2,13). Classically, DTI can be used to study the integrity and microstructure of white and gray matter at the cellular level by tracking of the mobility of water molecules. Neuronal architecture is organized as fiber bundles covered by dense myelin sheaths. These fiber tracts define the diffusion anisotropy of water. Decreased FA values indicate the tissue degeneration. Most of the DTI studies have focused on the subcortical gray matter nuclei but studying the FA level in substantia nigra can be promising (12,14).

A limited number of DTI studies have reported microstructural anomalies in PD. The decrease of FA in DTI is higher in PD compared to normal aging, and it is apparent in mesencephalon, thalamus and especially in SN (15). Nine meta-analysis covering 193 Parkinson patients and 195 control cases conclude that DTI can differentiate between the control group and PD (14). Consistent with the literature, FA was decreased in all regions that are studied in Parkinson patients compared to control group patients in the present study. Additionally, FA values of motor cortex, GPi, and GPe were decreased more on the left side in Parkinson patients. This can be related with being clinically affected of the right side dominantly in most of the cases.

Decreased FA is seen in brain regions, this can be related with demyelination that is seen with cell degeneration and loss (8,15). However, there are inconsistent results in the literature (12). In some studies, no significant difference between diffusion coefficient values in subcortical gray matter nuclei could be found, but usually these studies include late phase patients (1). Wen et al. have reported high FA values, but this study includes early PD patients (16). There are other studies that report no difference of FA values between PD and control groups (10). This can be related with the automatized (non-manual) selection of the regions for measurements. In the regions that white matter and grey matter differentiation is difficult, the automatized system can localize the measurements inappropriately, especially closer to the cortex. Axon and dendrite orientations are not normally aligned in the human cortex and FA measurements can be misleading in those regions (17,18). Some reports claim that DTI can differentiate between the motor subtypes of changes in SN (12,19). We could not make a subgroup analysis with our series due to the limited number of patients.

Studies evaluating brain activity in patients with Parkinson's disease demonstrated that cerebellum is continuously hyperactive during motor activities compared to healthy subjects. This is thought to be a compensatory mechanism against abnormally functioning basal ganglia. The increased metabolism in cerebellum was observed to be normalized in patients who received therapeutic stimulation. These studies support the idea that cerebellum might have an effect on motor signs of PD (20). In this study, FA values of the dentate nuclei was decreased but this finding was less noticeable than in basal ganglia.

Fractional anisotropy value measurement by DTI in SN is a good indicator for differentiating PD patients. Besides, there are studies suggesting its use to follow up disease progression. Parkinson disease patients must be evaluated when they are not on medications, and DTI should not be used in areas like the cerebral cortex where the white matter organization is not uniform (18).

White matter anomalies have been shown in PD without dementia (19). Studies are available in the literature directed to reveal the etiopathogenesis of PD. Generally, cortex or basal ganglia are assessed in these studies. Changes in different localizations including basal ganglia, cortex and cerebellum have been examined in this study, that should be considered as an advantage of our study.

Raw materials collected for DTI can be processed and encoded directionally to obtain a colored FA mapping. These colored FA mappings provide data with regard to anatomy. Diffusion Tensor Imaging has been proven to be valuable in the examination of white mater tracts and can be used in stereotactic or navigational targeting. Improvements in the anatomical identification of the main pathways in the subthalamic and globus pallidus regions will help patient specific fine targeting. Higher quality imaging might be important to reduce side effects associated with deep brain stimulation.

LIMITATIONS

Limitations of our study should be mentioned. First the number of patients included can be considered relatively small. Therefore, we could not be able to analyze the relationship between the FA values and disease duration, and subgroups of Parkinson syndromes. Compared to other functional imaging modalities (PET, SPECT), DTI has advantages including lower cost and higher spatial resolution. Moreover, FA analyses have an advantage of providing accurate measurements due to the simplicity, automatic nature and reproducibility of the results.

CONCLUSION

Decrease in FA measures in all regions compared to control group is thought to result from cellular loss in PD. Larger cohort studies are needed to determine if DTI can identify diffusion changes in very early phases of PD.

Our study demonstrated that the ability of DTI for visualization and quantification of white mater tracts specifically (globally and regionally) will allow patient specific anatomic targeting to augment the success of surgical treatments.

Competing Interests: All of the authors, but Atilla Yılmaz declare that they have no conflict of interest. Atilla Yilmaz have disclosures with Boston Scientific, Medtronic and Abbott in terms of proctorship.

Financial Disclosure: There are no financial supports.

Ethical Approval: The study was approved by the Okan University, School of Medicine, Ethical Review Board (20 November, 2019, Study no; 11-2019-115) and conducted in accordance with the declaration of Helsinki.

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