



# DTI Measurements for Huntington Disease Using Mricloud

Ayla Arslan<sup>1</sup>, Mehtap Nisari<sup>2</sup>, Emel Guler<sup>3</sup>, Gokce Bagci Uzun<sup>4</sup>, Murat Gultekin<sup>5</sup>, Halil Donmez<sup>6</sup>,  
 Keziban Bagci<sup>7</sup>, Niyazi Acer<sup>8</sup>

<sup>1</sup>Ağrı İbrahim Çeçen University, Faculty of Medicine, Department of Anatomy, Ağrı, Türkiye

<sup>2</sup>Erciyes University, Faculty of Medicine, Department of Anatomy, Kayseri, Türkiye

<sup>3</sup>Cumhuriyet University, Faculty of Medicine, Department of Physical Medicine and Rehabilitation, Algology, Sivas, Türkiye

<sup>4</sup>Malatya Turgut Özal University, Faculty of Medicine, Department of Anatomy, Malatya, Türkiye

<sup>5</sup>Erciyes University, Faculty of Medicine, Department of Neurology, Kayseri, Türkiye

<sup>6</sup>Erciyes University, Faculty of Medicine, Department of Radiology, Kayseri, Türkiye

<sup>7</sup>Niğde Ömer Halis Demir University, Niğde Zübeyde Hanım Vocational School of Health Services, Niğde, Türkiye

<sup>8</sup>Arel University, Faculty of Medicine, Department of Anatomy, İstanbul, Türkiye

Content of this journal is licensed under a Creative Commons Attribution-NonCommercial-NonDerivatives 4.0 International License.



## Abstract

**Aim:** Neurodegenerative diseases are important health problems that affect many people. In this study, it was aimed to examine the brain regions of Huntington's patients by performing brain parcellation.

**Material and Method:** 8 controls and 8 Huntington's patients participated in the study. We measured four Diffusion Tensor Imaging metrics which were axial diffusivity, mean diffusivity, radial diffusivity and fractional anisotropy performing brain parcellation over Diffusion Tensor Imaging for control and patient groups. We used a full automated data-driven approach to study the whole brain, divided in regions of interest using mricloud.

**Results:** When the huntington disease group compared to control group, We found that mean diffusivity and axial diffusivity increased frontal, parietal, temporal, occipital, corpus callosum, white matter, limbic and subcortical structures, and radial diffusivity increased corpus callosum, capsula interna ( $p<0.05$ ). The fractional anisotropy value was higher in nucleus caudatus, putamen and a significant difference was observed ( $p<0.05$ ).

**Conclusion:** The increase of axial diffusivity and mean diffusivity values axonal degeneration and demyelination of frontal, parietal, temporal, occipital, corpus callosum, white matter, limbic, subcortical structures; increased radial diffusivity values dysmyelination of the corpus callosum and capsula interna; fractional anisotropy increased values in nucleus caudatus and putamen may indicate a degenerative process, axon loss and inflammation.

**Keywords:** Huntington disease, neurodegenerative disease, brain, magnetic resonance imaging

## INTRODUCTION

Huntington's Disease (HD) is an inherited neurodegenerative illness lead to unusual enlargement of CAG (Cytosine-Adenine-Guanine) repetitions in the IT15 gene above chromosome (1). More than 36 CAG repetitions, particularly in the striatum, can cause brain atrophy and neuronal death. The main clinical characteristics of HD contain psychiatric disorders, cognitive disturbance and motor dysfunction (2). The basic pathology of HD is reduction of projection neurons, which can cause microstructural alterations or white matter abnormality in the striatum (3). Most of neuroimaging study in HD has focused on identifying biomarkers of disease course and brain imaging has helped explain the pathology in HD. Diffusion Tensor Imaging (DTI) is a process that shows

the direction of limitation of diffusion in tissue, which can also be expressed quantitatively. By measuring diffusion parameters such as axial diffusivity (AD), mean diffusivity (MD), radial diffusivity (RD) and fractional anisotropy (FA) via DTI, the direction and entirety of white matter tracts and also gray matter microstructure can be revealed (4,5). DTI works on HD indicated that psychiatric, cognitive signs of HD cases were related to impaired striatal structures like cortico-striatal circuits. Müller et al. stated that remarkable increase in FA value in subcortical nuclei in the patient group in terms of control group (6). Studies noticed that an increment FA worths in the putamen and nucleus caudate (7). Andica et al. stated that an increment in MD values and a decline in FA values in the nucleus caudatus in both HD patients and Pre-symptomatic (PreHD) patients

## CITATION

Arslan A, Nisari M, Guler E, et al. DTI Measurements for Huntington Disease Using Mricloud. Med Records. 2024;6(2):302-11. DOI:1037990/medr.1421420

Received: 17.01.2024 Accepted: 05.03.2024 Published: 16.05.2024

Corresponding Author: Mehtap Nisari, Erciyes University, Faculty of Medicine, Department of Anatomy, Kayseri, Türkiye

E-mail: mehtaph@erciyes.edu.tr

in comparison to controls. They also found a significant increment in AD and RD in corpus callosum in HD patients by comparison to controls. They also found a decline in FA worths in corpus callosum in preHD and HD by comparison to controls (8). Muhlau et al. realized that MD increment and FA decline in corpus callosum in the patient group in terms of control group (9). Zhang et al. found an increase RD, MD and AD values increased in capsula interna and capsula externa in the PreHD group than the control (10). Saba et al. realised that a remarkable decline in FA in the HD group in the corona radiata, corpus callosum, capsula externa, fasciculus longitudinalis superior and inferior, fasciculus frontooccipitalis compared to the control and preHD groups. They stated that the decrease in FA is an indicator of a degenerative process and axonal loss (11).

The aim of the study was to analyze each region of the brain in Huntington's patients using the brain parcellation method and to examine the effect of DTI parameters in these regions.

## MATERIAL AND METHOD

This study applied with the ratification of Erciyes University School of Medicine Clinical Research Ethics Committee dated 25.09.2019, decision number 2019/643. A control group of 8 people and 8 Huntington's patients participated in the study. The control group contained in the study consisted of men and women who did not have any neurological disease, had normal brain imaging, and were older than 18 years of age. The patient group joined in the study consisted of men and women who were diagnosed with Huntington's disease confirmed by genetic testing (with 40 or more CAG repeats) and who did not have any neurological disease other than Huntington's disease clinically and were aged 32-60 years (Table 1). DTI were obtained by obtaining the consents of the control and patient groups included in the study.

**Table 1. Demographic data of patient group**

Patient number	Gender	Age	CAG repeat	Disease duration
1	F	32	68	11 years
2	F	61	40	7 years
3	F	44	43	5 years
4	F	39	51	4 years
5	M	53	43	9 years
6	M	52	49	9 years
7	M	51	42	4 years
8	M	60	42	6 years

CAG: sitozin-adenin-guanin

In the study, FA, MD, RD, AD parameters were calculated by making brain parcellation on DTI for the control and patient groups.

### Sample

The specimen of this work was defined by power analysis.

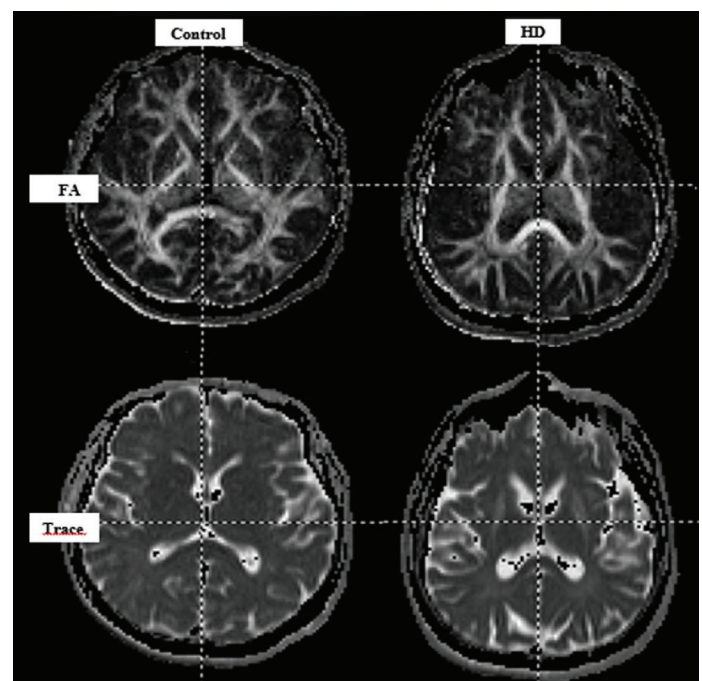
Based on the calculation using the G\*power 3.1 program. The sample dimension was stated as 16 (8 for each group) with an effect size of 1.4 a margin of error of 0.05, a confidence level of 0.80 and a population representation of 0.95 (12).

### Diffusion Tensor Imaging Protocol

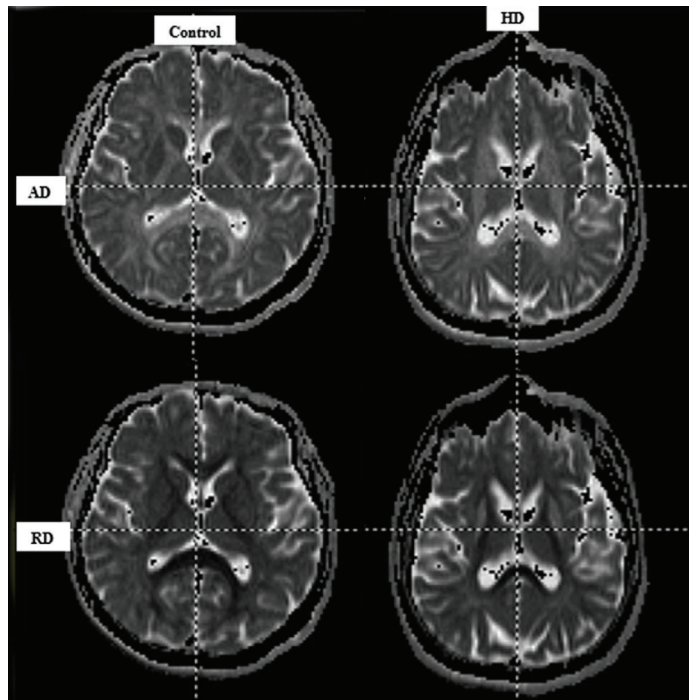
The DTI protocol used in the study consists of the following sequences:

- High resolution T1-weighted MPRAGE sequence to show the anatomical structure:** sagittal, Echo Time (TE)=2.67ms, Repetition time (TR)=1900ms, Matrix: 256x256, FOV=250mm, Slice Thickness=1mm.
- DTI:** axial, TR=3500ms, TE=83ms, number of sections=20, FOV=230mm, matrix: 128x128, section thickness=5mm, averages=3, b=0.1000 s/mm<sup>2</sup>, 20 diffusion directions.

In this study, we used MriStudio (<http://www.MriStudio.org>), an image processing system. The MR images were automatically segmented and postprocessed through MRICloud [[www.MRICloud.org](http://www.MRICloud.org)] (13-15). Mricloud is a public web-based service for multi-contrast imaging segmentation and quantification. The DTI segmentation involved image mapping based upon a set of linear algorithms and Large Deformation Diffeomorphic Mapping anisotropy, and eigen vector such as fiber orientation, and a final step of multi-atlas labeling fusion (16-18). The trace is expressed as the sum of the eigenvalues ( $\lambda_1+\lambda_2+\lambda_3$ ) and the mean diffusivity is their mean ( $=\text{trace}/3$ ). Eigenvalue1 ( $\lambda_1$ ) gives axial diffusivity. RD take the average of  $\lambda_2+\lambda_3$ . The index of the amount of diffusion asymmetry in the voxel ranging from 0 to 1 is defined as FA (19,20) (Figures 1 and 2) Maps were evaluated.



**Figure 1.** FA and MD maps in HD and control groups. FA: fractional anisotropy, MD: mean diffusivity, HD: Huntington's disease



**Figure 2.** AD, and RD maps in HD and control groups. AD: axial diffusivity, RD: radial diffusivity. HD: Huntington's disease

The following regions of interest (ROI) were automatically segmented and considered in further analysis: cerebral lobes (frontal, parietal, temporal, occipital and limbic), putamen, caudate nucleus, globus pallidus, thalamus, corpus callosum. In addition, the diffusion parameters (AD, MD, FA and RD) of each structure in the brain were calculated by making brain parcellation with mricloud (<https://braingps.mricloud.org/>).

### Subdivision mapping for DTI

1. DTIstudio was opened. DTI mapping from the file and whichever machine the image was taken from (Siemens, Philips etc.) was selected and automatic image registration and linear transformation were performed. After the process was completed, it was recorded in hdr format as FA, RD, ColorMap, MeanBO, Trace, Eigen Values and EigenVector.
2. ROleditor was opened. Then, statistical results of images such as FA, MD were obtained. MeanBO, FA and Trace images were recorded in hdr format as masked (21).

### Statistical analysis

The analysis of the datum contain in the work was made with the Statistics Program in Social Sciences (SPSS) 25 program. Shapiro Wilks Test was used to control whether the datum contain in the study fit the normal dispersion. The signification grade (p) for the comparison tests was determined as 0.05. Since the mutables did not posses a normal dispersion ( $p > 0.05$ ), the analysis was proceed with the non-parametric test method.

## RESULTS

The number of females and males of the patient (8) and control (8) groups included in the study was equal. Average

age; While it was 44 for women in the patient group, it was found to be 54 for men. The mean age of women in the control group was 56.5 and men 44.75.

AD, MD, RD and FA parameters of the brain regions were calculated individually by DT imaging in the control and patient groups (Tables 2-6).

For AD; SFG ( $p=0.001$ ), MFG ( $p=0.001$ ), IFG ( $p=0.001$ ), PrCG ( $p=0.002$ ), LFOG ( $p=0.001$ ), MFOG ( $p=0.007$ ), RG ( $p=0.001$ ), SPG ( $p=0.002$ ), PoCG ( $p=0.003$ ), AG ( $p=0.005$ ), PrCu ( $p=0.002$ ), SMG ( $p=0.001$ ), Cu ( $p=0.001$ ), LG ( $p=0.001$ ), SOG ( $p=0.001$ ), IOG ( $p=0.001$ ), MOG ( $p=0.001$ ), FuG ( $p=0.001$ ), ENT ( $p=0.006$ ), STG ( $p=0.002$ ), ITG ( $p=0.001$ ), MTG ( $p=0.001$ ). A statistical important dissimilarity was found through the groups (control and patient) (Table 2). For MD; SFG ( $p=0.001$ ), MFG ( $p=0.001$ ), IFG ( $p=0.001$ ), PrCG ( $p=0.001$ ), LFOG ( $p=0.001$ ), MFOG ( $p=0.014$ ), RG ( $p=0.001$ ), SPG ( $p=0.001$ ), PoCG ( $p=0.002$ ), AG ( $p=0.002$ ), PrCu ( $p=0.002$ ), SMG ( $p=0.001$ ), Cu ( $p=0.001$ ), LG ( $p=0.001$ ), SOG ( $p=0.001$ ), IOG ( $p=0.001$ ), MOG ( $p=0.001$ ), FuG ( $p=0.001$ ), ENT ( $p=0.006$ ), STG ( $p=0.002$ ), ITG ( $p=0.001$ ), MTG ( $p=0.001$ ) = 0.001, a statistical important dissimilarity was found through the groups (control and patient) (Table 2). For RD; SFG ( $p=0.012$ ), MFG ( $p=0.012$ ), IFG ( $p=0.012$ ), PrCG ( $p=0.016$ ), LFOG ( $p=0.012$ ), RG ( $p=0.016$ ), SPG ( $p=0.012$ ), PoCG ( $p=0.016$ ), AG ( $p=0.021$ ), PrCu ( $p=0.027$ ), SMG ( $p=0.012$ ), Cu ( $p=0.012$ ), LG ( $p=0.012$ ), SOG ( $p=0.012$ ), IOG ( $p=0.012$ ), MOG ( $p=0.012$ ), FuG ( $p=0.012$ ), STG ( $p=0.021$ ), ITG ( $p=0.016$ ), MTG ( $p=0.012$ ) a statistical important through the groups (patient and control) in measures dissimilarity was found (Table 2). There was no statistical important dissimilarity through the groups (patient and control) in FA measures ( $p > 0.05$ ) (Table 2).

For AD; A statistical meaningful dissimilarity was found through the groups (patient and control) in GCC ( $p=0.001$ ), SCC ( $p=0.001$ ) measures (Table 3). For MD; A statistically meaningful dissimilarity was found between the groups (patient and control) in GCC ( $p=0.001$ ), BCC ( $p=0.009$ ), SCC ( $p=0.001$ ) measurements (Table 3). For RD; A statistical meaningful dissimilarity was found through the groups (patient and control) in GCC ( $p=0.009$ ) and SCC ( $p=0.009$ ) measures (Table 3). There was no statistical important dissimilarity through the groups (patient and control) in FA measures ( $p > 0.05$ ) (Table 3).

For AD; CingG ( $p=0.001$ ), Ins ( $p=0.002$ ), Amyg ( $p=0.001$ ), Hippo ( $p=0.002$ ), FxST ( $p=0.003$ ), H ( $p=0.003$ ), NIM ( $p=0.018$ ). A statistical significant dissimilarity was found through groups (patient and control) (Table 4). For MD; CingG ( $p=0.001$ ), PHG ( $p=0.045$ ), Ins ( $p=0.002$ ), Amyg ( $p=0.002$ ), Hippo ( $p=0.002$ ), FxST ( $p=0.005$ ), H ( $p=0.002$ ), NIM ( $p=0.016$ ). A statistical significant dissimilarity was found through the groups (patient and control) in measurements (Table 4). For RD; CingG ( $p=0.012$ ), PHG ( $p=0.018$ ), Ins ( $p=0.027$ ), Amyg ( $p=0.027$ ), Hippo ( $p=0.021$ ), FxST ( $p=0.027$ ), H ( $p=0.012$ ). A statistical important difference was found through the groups (patient and control) (Table 4). No statistical important dissimilarity through the groups (patient and control) in FA measures ( $p > 0.05$ ) (Table 4).

Table 2. AD, MD, RD, FA values of the structures in the frontal, parietal, occipital, temporal lobes

Variables	Groups	AD			MD			RD			FA		
		Mean±sd	M (Min-Max)	p value	Mean±sd	M (Mi-Max)	p value	Mean±sd	M (Min-Max)	p value	Mean±sd	M (Min-Max)	p value
SFG	Patient	1.21±0.07	1.23 (1.11-1.32)	0.001*	1.01±0.06	1.02 (0.93-1.1)	0.001*	0.81±0.24	0.89 (0.23-0.96)	0.012*	0.22±0.02	0.22 (0.2-0.26)	0.674
	Control	1.03±0.05	1.02 (0.96-1.1)		0.85±0.04	0.84 (0.78-0.92)		0.76±0.04	0.75 (0.7-0.83)		0.21±0.04	0.23 (0.15-0.24)	
MFG	Patient	1.29±0.08	1.31 (1.18-1.4)	0.001*	1.1±0.07	1.11 (1.01-1.19)	0.001*	0.9±0.29	0.99 (0.2-1.08)	0.012*	0.19±0.01	0.19 (0.18-0.22)	0.834
	Control	1.09±0.05	1.08 (1.03-1.16)		0.92±0.04	0.91 (0.87-0.98)		0.83±0.04	0.82 (0.79-0.89)		0.19±0.03	0.2 (0.14-0.22)	
IFG	Patient	1.25±0.06	1.25 (1.16-1.33)	0.001*	1.05±0.06	1.04 (0.97-1.13)	0.001*	0.85±0.26	0.92 (0.21-1.03)	0.012*	0.21±0.01	0.21 (0.2-0.24)	0.141
	Control	1.06±0.05	1.05 (1.01-1.15)		0.87±0.05	0.85 (0.82-0.96)		0.77±0.05	0.75 (0.72-0.86)		0.21±0.04	0.24 (0.14-0.25)	
PrCG	Patient	1.15±0.05	1.15 (1.09-1.22)	0.002*	0.91±0.04	0.9 (0.86-0.98)	0.001*	0.72±0.18	0.77 (0.28-0.85)	0.016*	0.27±0.02	0.27 (0.24-0.32)	0.401
	Control	1.03±0.04	1.03 (0.98-1.1)		0.79±0.04	0.79 (0.75-0.86)		0.67±0.04	0.67 (0.64-0.74)		0.26±0.06	0.29 (0.17-0.31)	
LFOG	Patient	1.27±0.05	1.28 (1.2-1.34)	0.001*	1.09±0.05	1.07 (1.04-1.17)	0.001*	0.89±0.3	0.97 (0.17-1.08)	0.012*	0.18±0.02	0.17 (0.16-0.22)	0.636
	Control	1.1±0.05	1.1 (1.04-1.19)		0.92±0.05	0.92 (0.87-1.02)		0.84±0.05	0.84 (0.79-0.93)		0.17±0.04	0.19 (0.1-0.2)	
MFOG	Patient	1.27±0.06	1.26 (1.2-1.36)	0.007*	1.09±0.05	1.07 (1.03-1.17)	0.014*	0.89±0.3	0.97 (0.16-1.08)	0.141	0.17±0.03	0.16 (0.15-0.24)	0.916
	Control	1.14±0.07	1.11 (1.07-1.27)		0.98±0.07	0.95 (0.91-1.1)		0.9±0.07	0.87 (0.84-1.02)		0.15±0.04	0.17 (0.09-0.18)	
RG	Patient	1.22±0.04	1.21 (1.16-1.28)	0.001*	1.06±0.04	1.06 (1.02-1.14)	0.001*	0.87±0.3	0.97 (0.13-1.03)	0.016*	0.15±0.02	0.15 (0.13-0.19)	0.753
	Control	1.07±0.06	1.07 (0.98-1.18)		0.93±0.06	0.93 (0.85-1.03)		0.86±0.05	0.87 (0.78-0.96)		0.14±0.03	0.16 (0.09-0.17)	
SPG	Patient	1.33±0.07	1.35 (1.23-1.43)	0.002*	1.08±0.06	1.1 (0.99-1.17)	0.001*	0.86±0.25	0.94 (0.26-0.99)	0.012*	0.26±0.02	0.25 (0.23-0.3)	0.208
	Control	1.15±0.06	1.15 (1.07-1.24)		0.9±0.05	0.9 (0.84-0.99)		0.78±0.05	0.77 (0.72-0.86)		0.26±0.05	0.28 (0.17-0.3)	
PoCG	Patient	1.42±0.11	1.46 (1.24-1.53)	0.003*	1.22±0.1	1.26 (1.08-1.32)	0.002*	1±0.34	1.09 (0.19-1.23)	0.016*	0.19±0.02	0.19 (0.16-0.23)	0.916
	Control	1.18±0.08	1.16 (1.08-1.28)		1.01±0.07	0.98 (0.92-1.1)		0.92±0.07	0.89 (0.84-1.02)		0.18±0.03	0.19 (0.14-0.21)	
AG	Patient	1.41±0.11	1.43 (1.24-1.52)	0.005*	1.21±0.1	1.24 (1.07-1.32)	0.002*	0.99±0.33	1.09 (0.19-1.22)	0.021*	0.18±0.02	0.18 (0.16-0.22)	0.462
	Control	1.18±0.07	1.16 (1.08-1.28)		1±0.07	0.98 (0.91-1.09)		0.91±0.07	0.89 (0.82-0.99)		0.18±0.03	0.19 (0.13-0.2)	
PrCu	Patient	1.46±0.12	1.45 (1.28-1.6)	0.002*	1.29±0.11	1.29 (1.14-1.43)	0.002*	1.06±0.38	1.15 (0.14-1.32)	0.027*	0.15±0.01	0.15 (0.14-0.16)	0.834
	Control	1.2±0.08	1.18 (1.12-1.32)		1.06±0.07	1.04 (0.98-1.17)		0.99±0.07	0.97 (0.91-1.1)		0.14±0.03	0.15 (0.09-0.16)	
SMG	Patient	1.33±0.08	1.33 (1.22-1.45)	0.001*	1.15±0.07	1.15 (1.07-1.26)	0.001*	0.93±0.31	1.02 (0.18-1.11)	0.012*	0.18±0.02	0.18 (0.15-0.22)	0.294
	Control	1.12±0.07	1.11 (1.05-1.24)		0.95±0.06	0.94 (0.87-1.05)		0.86±0.06	0.85 (0.79-0.96)		0.18±0.03	0.2 (0.13-0.2)	
Cu	Patient	1.41±0.08	1.43 (1.32-1.52)	0.001*	1.24±0.08	1.25 (1.12-1.34)	0.001*	1.03±0.36	1.16 (0.16-1.25)	0.012*	0.16±0.02	0.16 (0.13-0.2)	0.248
	Control	1.15±0.06	1.17 (1.03-1.23)		0.98±0.05	0.98 (0.88-1.05)		0.89±0.05	0.89 (0.8-0.96)		0.17±0.04	0.18 (0.1-0.2)	

sd: standard deviation, M: median, p: Mann Whitney U test significance value. \*p<0.05; there is a statistically significant difference between the groups. SFG: gyrus frontalis superior, MFG: gyrus frontalis medius, IFG: gyrus frontalis inferior, Pr: CG: gyrus precentralis, LFOG: gyrus fronto-orbitalis lateralis, MFOG: gyrus fronto-orbitalis medius, RG: gyrus rectus, SPG: lobulus parietalis superior, Po: CG: gyrus postcentralis, AG: gyrus angularis, Pr: Cu: precuneus, SMG: gyrus supramarginalis, SOG: gyri occipitalis superior, IOG: gyri occipitalis inferior, MOG: gyri occipitalis medius, FUG: gyrus fusiformis, ENT: cortex entorhinalis, STG: gyrus temporalis superior, ITG-: gyrus temporalis inferior, MTG: gyrus temporalis medius

Table 2. AD, MD, RD, FA values of the structures in the frontal, parietal, occipital, temporal lobes

LG	Patient	Mean±sd	M (Min-Max)	p value	Mean±sd	M (Min-Max)	p value	Mean±sd	M (Min-Max)	p value	Mean±sd	M (Min-Max)	p value	Mean±sd	M (Min-Max)	p value
LG	Patient	1.36±0.08	1.36 (1.25-1.48)	<b>0.001*</b>	1.18±0.08	1.18 (1.08-1.29)	<b>0.001*</b>	0.97±0.34	1.07 (0.15-1.19)	<b>0.012*</b>	0.16±0.02	0.16 (0.15-0.2)	<b>0.012*</b>	0.17±0.04	0.19 (0.11-0.2)	0.401
	Control	1.11±0.06	1.13 (1-1.19)		0.94±0.06	0.96 (0.85-1.03)		0.86±0.06	0.87 (0.77-0.95)		0.23±0.02	0.23 (0.21-0.27)	<b>0.012*</b>	0.23±0.04	0.24 (0.16-0.27)	0.916
SOG	Patient	1.29±0.06	1.31 (1.21-1.38)	<b>0.001*</b>	1.06±0.06	1.07 (0.98-1.14)	<b>0.001</b>	0.86±0.26	0.92 (0.24-1.03)	<b>0.012*</b>	0.16±0.02	0.16 (0.14-0.22)	<b>0.012*</b>	0.17±0.04	0.19 (0.1-0.2)	0.294
	Control	1.11±0.08	1.12 (0.96-1.2)		0.89±0.07	0.9 (0.77-0.97)		0.91±0.31	0.98 (0.16-1.12)	<b>0.012*</b>	0.23±0.04	0.24 (0.16-0.27)		0.23±0.04	0.24 (0.16-0.27)	
IOG	Patient	1.27±0.07	1.29 (1.17-1.38)	<b>0.001*</b>	1.1±0.06	1.09 (1.03-1.21)	<b>0.001*</b>	0.81±0.06	0.82 (0.71-0.9)	<b>0.012*</b>	0.16±0.02	0.16 (0.14-0.22)	<b>0.012*</b>	0.17±0.04	0.19 (0.1-0.2)	0.294
	Control	1.06±0.06	1.07 (0.96-1.15)		0.89±0.06	0.9 (0.8-0.98)		0.81±0.06	0.82 (0.71-0.9)		0.16±0.02	0.16 (0.14-0.22)		0.17±0.04	0.19 (0.1-0.2)	
MOG	Patient	1.36±0.09	1.36 (1.27-1.51)	<b>0.001*</b>	1.18±0.09	1.18 (1.06-1.32)	<b>0.001*</b>	0.98±0.33	1.07 (0.18-1.22)	<b>0.012*</b>	0.17±0.02	0.16 (0.15-0.21)	<b>0.012*</b>	0.17±0.02	0.16 (0.15-0.21)	0.345
	Control	1.1±0.06	1.1 (1.02-1.19)		0.93±0.05	0.93 (0.85-1.01)		0.84±0.05	0.84 (0.77-0.92)		0.17±0.02	0.16 (0.15-0.21)		0.17±0.04	0.19 (0.11-0.2)	
FuG	Patient	1.26±0.08	1.25 (1.16-1.42)	<b>0.001*</b>	1.08±0.07	1.07 (1-1.24)	<b>0.001*</b>	0.9±0.3	0.97 (0.17-1.15)	<b>0.012*</b>	0.17±0.02	0.17 (0.16-0.21)	<b>0.012*</b>	0.17±0.02	0.18 (0.1-0.2)	0.345
	Control	1.07±0.05	1.07 (0.99-1.13)		0.9±0.05	0.91 (0.82-0.97)		0.82±0.05	0.83 (0.74-0.89)		0.17±0.02	0.17 (0.16-0.21)		0.17±0.04	0.18 (0.1-0.2)	
ENT	Patient	1.41±0.26	1.47 (1.03-1.67)	<b>0.006*</b>	1.2±0.23	1.24 (0.87-1.45)	<b>0.006*</b>	0.98±0.39	1.07 (0.17-1.34)	0.052	0.17±0.02	0.18 (0.14-0.21)		0.15±0.06	0.18 (0.05-0.19)	0.834
	Control	1.04±0.09	1.02 (0.94-1.19)		0.88±0.08	0.86 (0.78-1)		0.79±0.07	0.78 (0.69-0.91)		0.17±0.02	0.18 (0.14-0.21)		0.15±0.06	0.18 (0.05-0.19)	
STG	Patient	1.38±0.09	1.41 (1.24-1.48)	<b>0.002*</b>	1.19±0.08	1.21 (1.08-1.29)	<b>0.002*</b>	0.98±0.33	1.08 (0.17-1.19)	<b>0.021*</b>	0.17±0.01	0.17 (0.16-0.2)	<b>0.021*</b>	0.17±0.03	0.19 (0.12-0.19)	0.294
	Control	1.15±0.08	1.15 (1.04-1.28)		0.98±0.07	0.98 (0.88-1.11)		0.9±0.07	0.9 (0.8-1.02)		0.17±0.01	0.17 (0.16-0.2)		0.17±0.03	0.19 (0.12-0.19)	
ITG	Patient	1.19±0.06	1.2 (1.1-1.26)	<b>0.001*</b>	1±0.05	1 (0.92-1.06)	<b>0.001*</b>	0.81±0.25	0.89 (0.19-0.96)	<b>0.016*</b>	0.2±0.02	0.2 (0.19-0.24)	<b>0.016*</b>	0.18±0.05	0.2 (0.1-0.23)	0.401
	Control	1.07±0.02	1.2 (1.04-1.1)		0.89±0.03	1 (0.84-0.93)		0.79±0.03	0.89 (0.75-0.84)		0.2±0.02	0.2 (0.19-0.24)		0.18±0.05	0.2 (0.1-0.23)	
MTG	Patient	1.21±0.05	1.06 (1.14-1.27)	<b>0.001*</b>	1.03±0.04	0.88 (0.98-1.09)	<b>0.001*</b>	0.85±0.27	0.79 (0.18-1)	<b>0.012*</b>	0.18±0.02	0.21 (0.16-0.21)	<b>0.012*</b>	0.18±0.02	0.21 (0.16-0.21)	0.345
	Control	1.02±0.18	1.22 (0.57-1.14)		0.9±0.04	1.04 (0.84-0.97)		0.82±0.04	0.92 (0.75-0.88)		0.18±0.02	0.21 (0.16-0.21)		0.17±0.04	0.18 (0.11-0.2)	

sd: standard deviation, M: median, p: Mann Whitney U test significance value. \*p<0.05; there is a statistically significant difference between the groups. SFG: gyrus frontalis superior, MFG: gyrus frontalis medius, IFG: gyrus frontalis inferior, Pr. CG: gyrus precentralis, LFOG: gyrus frontoorbitalis lateralis, MFOG: gyrus frontoorbitalis medius, RCG: gyrus rectus, SPG: lobulus parietalis superior, Po. CG: gyrus postcentralis, AG: gyrus angularis, Pr. Cu: cuneus, SMG: gyrus supramarginalis, Cu: cuneus, LF: fasciculus lenticularis, SOG: gyri occipitalis superior, IOG: gyri occipitalis inferior, MOG: gyri occipitalis medius, FUG: gyrus fusiformis, ENT: cortex entorhinalis, STG: gyrus temporalis superior, ITG: gyrus temporalis inferior, MTG: gyrus temporalis medius

Table 3. AD, MD, RD, FA values of structures in corpus callosum

Variables	Groups	AD			MD			RD			FA					
		Mean±sd	M (Min-Max)	p value	Mean±sd	M (Min-Max)	p value	Mean±sd	M (Min-Max)	p value	Mean±sd	M (Min-Max)	p value			
GCC	Patient	1.71±0.06	1.71 (1.64-1.79)	<b>0.001*</b>	1.09±0.08	1.08 (1.01-1.22)	<b>0.001*</b>	0.75±0.13	0.73 (0.51-0.94)	<b>0.009*</b>	0.49±0.03	0.51 (0.44-0.53)	<b>0.009*</b>	0.48±0.17	0.55 (0.2-0.61)	0.093
	Control	1.57±0.05	1.59 (1.5-1.62)		0.93±0.05	0.93 (0.84-0.97)		0.6±0.05	0.62 (0.51-0.65)		0.47±0.03	0.47 (0.44-0.53)		0.47±0.03	0.5 (0.17-0.56)	0.401
BCC	Patient	1.66±0.07	1.64 (1.56-1.8)	0.059	1.06±0.05	1.05 (1-1.12)	<b>0.009*</b>	0.72±0.11	0.75 (0.46-0.83)	0.115	0.47±0.03	0.47 (0.44-0.53)	0.115	0.43±0.16	0.5 (0.17-0.56)	0.401
	Control	1.58±0.07	1.6 (1.45-1.64)		0.98±0.05	0.99 (0.92-1.06)		0.68±0.05	0.67 (0.63-0.77)		0.47±0.03	0.47 (0.44-0.53)		0.43±0.16	0.5 (0.17-0.56)	
SCC	Patient	1.73±0.03	1.72 (1.69-1.8)	<b>0.001*</b>	1.05±0.04	1.04 (1-1.12)	<b>0.001*</b>	0.69±0.08	0.7 (0.54-0.8)	<b>0.009*</b>	0.53±0.02	0.53 (0.48-0.56)	<b>0.009*</b>	0.49±0.17	0.58 (0.21-0.62)	0.093
	Control	1.6±0.06	1.59 (1.5-1.7)		0.92±0.05	0.91 (0.86-0.99)		0.58±0.04	0.57 (0.53-0.64)		0.53±0.02	0.53 (0.48-0.56)		0.49±0.17	0.58 (0.21-0.62)	

sd: standard deviation, M: median, p: Mann Whitney U test significance value. \*p<0.05; there is a statistically significant difference between the groups. GCC: genu corporis callosi, BCC: truncus corporis callosi, SCC: splenium corporis callosi, CGC: genu corporis callosi, GCC: genu corporis callosi, BCC: truncus corporis callosi, SCC: splenium corporis callosi

Table 4. AD, MD, RD, FA values of structures in the limbic lobe

Variables	Groups	AD			MD			RD			FA		
		Mean±sd	M (Min-Max)	p value	Mean±sd	M (Min-Max)	p value	Mean±sd	M (Min-Max)	p value	Mean±sd	M (Min-Max)	p value
CingG	Patient	1.25±0.06	1.24 (1.18-1.34)	<b>0.001*</b>	1.09±0.05	1.08 (1.03-1.17)	<b>0.001*</b>	1.01±0.05	1.01 (0.96-1.09)	<b>0.012*</b>	0.16±0.01	0.16 (0.15-0.19)	0.529
	Control	1.05±0.05	1.04 (1-1.13)		0.9±0.04	0.89 (0.86-0.98)		0.83±0.04	0.81 (0.78-0.9)		0.16±0.03	0.17 (0.11-0.17)	
PHG	Patient	1.83±0.4	1.79 (1.33-2.31)	0.068	1.58±0.36	1.57 (1.15-2.08)	<b>0.045*</b>	1.45±0.34	1.46 (1.06-1.95)	<b>0.018*</b>	0.17±0.04	0.17 (0.13-0.23)	0.201
	Control	1.43±0.15	1.42 (1.27-1.65)		1.18±0.14	1.17 (1.01-1.38)		1.03±0.13	1.04 (0.88-1.25)		0.2±0.06	0.21 (0.09-0.24)	
Ins	Patient	1.29±0.09	1.25 (1.21-1.42)	<b>0.002*</b>	1.11±0.07	1.08 (1.05-1.21)	<b>0.002*</b>	1.03±0.06	0.99 (0.97-1.11)	<b>0.027*</b>	0.17±0.01	0.16 (0.16-0.18)	0.674
	Control	1.09±0.04	1.1 (1.04-1.15)		0.93±0.04	0.94 (0.88-0.99)		0.85±0.04	0.85 (0.81-0.91)		0.16±0.04	0.17 (0.09-0.18)	
Amyg	Patient	1.22±0.02	1.21 (1.19-1.25)	<b>0.001*</b>	1.02±0.03	1.01 (0.99-1.06)	<b>0.002*</b>	0.92±0.04	0.91 (0.87-0.96)	<b>0.027*</b>	0.19±0.03	0.19 (0.16-0.24)	0.674
	Control	1.07±0.03	1.08 (1.02-1.1)		0.88±0.03	0.9 (0.84-0.91)		0.79±0.03	0.81 (0.75-0.82)		0.18±0.05	0.2 (0.08-0.2)	
Hippo	Patient	1.5±0.08	1.54 (1.4-1.58)	<b>0.002*</b>	1.25±0.07	1.26 (1.17-1.34)	<b>0.002*</b>	1.13±0.07	1.12 (1.06-1.22)	<b>0.021*</b>	0.19±0.02	0.18 (0.18-0.22)	0.401
	Control	1.22±0.09	1.2 (1.11-1.35)		1±0.08	0.98 (0.91-1.12)		0.89±0.08	0.87 (0.81-1)		0.19±0.04	0.21 (0.11-0.22)	
FxFST	Patient	1.58±0.07	1.58 (1.5-1.68)	<b>0.003*</b>	1.1±0.03	1.09 (1.08-1.14)	<b>0.005*</b>	0.86±0.04	0.87 (0.82-0.91)	<b>0.027*</b>	0.39±0.03	0.41 (0.34-0.42)	0.674
	Control	1.4±0.1	1.41 (1.27-1.52)		0.92±0.06	0.93 (0.82-0.99)		0.68±0.05	0.69 (0.6-0.74)		0.39±0.13	0.43 (0.12-0.46)	
Fx	Patient	2.36±0.27	2.45 (1.88-2.52)	0.115	1.65±0.37	1.76 (1.01-1.91)	0.059	1.4±0.55	1.41 (0.57-2.07)	0.294	0.42±0.14	0.38 (0.3-0.65)	0.294
	Control	2.23±0.31	2.25 (1.77-2.57)		1.47±0.33	1.54 (1.03-1.82)		1.1±0.36	1.12 (0.66-1.58)		0.45±0.17	0.51 (0.13-0.58)	
H	Patient	1.52±0.15	1.45 (1.36-1.71)	<b>0.003*</b>	1.19±0.09	1.15 (1.12-1.34)	<b>0.002*</b>	1.03±0.07	1 (0.96-1.15)	<b>0.012*</b>	0.27±0.04	0.27 (0.21-0.31)	0.172
	Control	1.08±0.28	1.12 (0.59-1.44)		0.9±0.11	0.86 (0.81-1.1)		0.77±0.1	0.74 (0.68-0.93)		0.24±0.09	0.26 (0.08-0.32)	
NIM	Patient	1.1±0.05	1.09 (1.05-1.17)	<b>0.018*</b>	0.88±0.03	0.88 (0.82-0.91)	<b>0.016*</b>	0.76±0.04	0.77 (0.71-0.8)	0.093	0.25±0.05	0.23 (0.21-0.32)	0.529
	Control	1.02±0.04	1.03 (0.94-1.05)		0.77±0.02	0.77 (0.73-0.79)		0.65±0.02	0.64 (0.62-0.68)		0.27±0.07	0.28 (0.14-0.32)	

sd: standard deviation, M: median, p: Mann Whitney U test significance value, \*p<0.05; there is a statistically significant difference between the groups. CingG: gyrus cinguli, PHG: gyrus parahippocampalis, Ins: insula, Amyg: amygdala, Hippo: hippocampus, Fx/ST: fornix-stria terminalis, Fx: fornix, H: hypothalamus, NIM: nucleus innominata

Table 5. AD, MD, RD, FA values of fascicles found in white matter

Variables	Groups	AD			MD			RD			FA		
		Mean±sd	M (Min-Max)	p value	Mean±sd	M (Min-Max)	p value	Mean±sd	M (Min-Max)	p value	Mean±sd	M (Min-Max)	p value
SLF	Patient	1.16±0.04	1.18 (1.1-1.19)	<b>0.001*</b>	0.83±0.03	0.85 (0.78-0.87)	<b>0.001*</b>	0.63±0.11	0.67 (0.36-0.72)	<b>0.016*</b>	0.36±0.01	0.36 (0.34-0.38)	0.172
	Control	1.04±0.03	1.05 (0.99-1.07)		0.74±0.03	0.74 (0.7-0.78)		0.59±0.03	0.58 (0.55-0.63)		0.32±0.13	0.38 (0.11-0.4)	
IFO	Patient	1.26±0.04	1.25 (1.2-1.33)	<b>0.001*</b>	0.87±0.03	0.88 (0.84-0.92)	<b>0.001*</b>	0.65±0.11	0.69 (0.38-0.72)	<b>0.012*</b>	0.39±0.02	0.38 (0.37-0.42)	1.000
	Control	1.16±0.04	1.17 (1.08-1.19)		0.78±0.03	0.78 (0.73-0.81)		0.59±0.03	0.59 (0.55-0.63)		0.34±0.12	0.4 (0.15-0.44)	
UNC	Patient	1.28±0.06	1.25 (1.2-1.38)	<b>0.016*</b>	0.93±0.04	0.92 (0.88-1.02)	<b>0.001*</b>	0.7±0.15	0.75 (0.33-0.78)	<b>0.024*</b>	0.34±0.03	0.33 (0.3-0.37)	0.753
	Control	1.2±0.04	1.18 (1.16-1.25)		0.85±0.03	0.84 (0.82-0.88)		0.67±0.03	0.66 (0.64-0.72)		0.3±0.11	0.36 (0.12-0.39)	
SS	Patient	1.36±0.05	1.36 (1.29-1.45)	<b>0.001*</b>	0.96±0.04	0.97 (0.88-1.01)	<b>0.002*</b>	0.72±0.14	0.78 (0.39-0.79)	<b>0.021*</b>	0.38±0.02	0.39 (0.35-0.42)	0.294
	Control	1.24±0.05	1.25 (1.16-1.32)		0.84±0.05	0.83 (0.78-0.93)		0.64±0.06	0.63 (0.58-0.73)		0.35±0.14	0.43 (0.12-0.44)	

sd: standard deviation, M: Median, p: Mann Whitney U test significance value, \*p<0.05; there is a statistically significant difference between the groups. SLF: sacculus longitudinalis superior IFO: fasciculus frontooccipitalis inferior UNC: fasciculus uncinatus SS: sagittal stratum ACR: anterior corona radiata SCR: superior corona radiata PCR: posterior corona radiata

Table 5. AD, MD, RD, FA values of fascicles found in white matter

Variables	Groups	Mean±sd	M (Min-Max)	p value	Mean±sd	M (Min-Max)	p value	Mean±sd	M (Min-Max)	p value	Mean±sd	M (Min-Max)	p value
ACR	Patient	1.22±0.03	1.22 (1.17-1.27)	<b>0.001*</b>	0.85±0.03	0.85 (0.81-0.91)	<b>0.001*</b>	0.64±0.1	0.65 (0.4-0.74)	<b>0.012*</b>	0.39±0.03	0.39 (0.34-0.42)	0.753
	Control	1.1±0.03	1.1 (1.05-1.14)		0.75±0.03	0.76 (0.7-0.79)		0.58±0.03	0.58 (0.52-0.62)		0.34±0.13	0.39 (0.12-0.43)	
SCR	Patient	1.17±0.03	1.18 (1.11-1.19)	<b>0.001*</b>	0.79±0.03	0.8 (0.75-0.84)	<b>0.001*</b>	0.58±0.08	0.59 (0.42-0.67)	<b>0.021*</b>	0.41±0.03	0.42 (0.36-0.47)	0.916
	Control	1.06±0.04	1.07 (1-1.11)		0.71±0.03	0.72 (0.68-0.75)		0.54±0.02	0.54 (0.5-0.57)		0.35±0.14	0.42 (0.13-0.45)	
PCR	Patient	1.28±0.06	1.27 (1.18-1.37)	<b>0.002*</b>	0.86±0.04	0.86 (0.81-0.91)	<b>0.001*</b>	0.63±0.09	0.65 (0.43-0.7)	<b>0.046*</b>	0.42±0.03	0.42 (0.39-0.47)	0.208
	Control	1.13±0.05	1.12 (1.08-1.22)		0.76±0.04	0.76 (0.72-0.81)		0.58±0.03	0.58 (0.55-0.63)		0.35±0.14	0.42 (0.12-0.44)	

sd: standard deviation, M: Median, p: Mann Whitney U test significance value, \*p<0.05; there is a statistically significant difference between the groups. SLF: sacculus longitudinalis superior IFO: fasciculus frontooccipitalis inferior UNC: fasciculus uncinatus SS: sagittal stratum ACR: anterior corona radiata SCR: superior corona radiata PCR: posterior corona radiata

Table 6. AD, MD, RD, FA values of structures in the subcortical region

Variables	Groups	Mean±sd	M (Min-Max)	p value	Mean±sd	M (Min-Max)	p value	Mean±sd	M (Min-Max)	p value	Mean±sd	M (Min-Max)	p value
ALIC	Patient	1.36±0.07	1.32 (1.28-1.46)	<b>0.001*</b>	0.86±0.06	0.83 (0.8-0.94)	<b>0.001*</b>	0.6±0.07	0.6 (0.5-0.67)	<b>0.003*</b>	0.49±0.03	0.48 (0.45-0.52)	0.674
	Control	1.16±0.04	1.15 (1.1-1.21)		0.72±0.02	0.72 (0.69-0.73)		0.49±0.01	0.49 (0.47-0.51)		0.5±0.02	0.49 (0.48-0.52)	
PLIC	Patient	1.41±0.03	1.41 (1.36-1.44)	<b>0.001*</b>	0.81±0.03	0.82 (0.77-0.84)	<b>0.001*</b>	0.53±0.05	0.54 (0.45-0.58)	<b>0.012*</b>	0.58±0.03	0.57 (0.55-0.63)	0.753
	Control	1.25±0.03	1.24 (1.22-1.31)		0.72±0.02	0.72 (0.69-0.74)		0.45±0.02	0.45 (0.43-0.48)		0.58±0.01	0.58 (0.55-0.59)	
RLIC	Patient	1.4±0.03	1.4 (1.38-1.45)	<b>0.001*</b>	0.89±0.03	0.91 (0.84-0.91)	<b>0.001*</b>	0.61±0.08	0.65 (0.48-0.67)	<b>0.027*</b>	0.48±0.03	0.48 (0.45-0.53)	0.834
	Control	1.22±0.03	1.22 (1.18-1.27)		0.77±0.02	0.77 (0.74-0.79)		0.55±0.02	0.54 (0.51-0.58)		0.49±0.02	0.49 (0.46-0.51)	
Snigra	Patient	1.43±0.59	1.3 (0.98-2.45)	0.584	0.97±0.48	0.78 (0.71-1.82)	1.000	0.69±0.47	0.58 (0.37-1.51)	0.715	0.44±0.15	0.39 (0.29-0.69)	0.465
	Control	1.16±0.08	1.14 (1.08-1.3)		0.77±0.03	0.77 (0.74-0.8)		0.57±0.07	0.57 (0.46-0.65)		0.46±0.08	0.44 (0.38-0.6)	
Caud	Patient	1.4±0.16	1.36 (1.25-1.64)	<b>0.001*</b>	1.15±0.14	1.09 (1.02-1.36)	<b>0.001*</b>	0.88±0.37	0.94 (0.26-1.21)	<b>0.01*2</b>	0.24±0.02	0.23 (0.21-0.26)	<b>0.005*</b>
	Control	0.98±0.03	0.97 (0.95-1.02)		0.81±0.02	0.81 (0.78-0.84)		0.73±0.02	0.73 (0.69-0.76)		0.21±0.01	0.2 (0.19-0.23)	
Put	Patient	1.21±0.07	1.16 (1.15-1.3)	<b>0.001*</b>	0.99±0.06	0.97 (0.91-1.05)	<b>0.001*</b>	0.74±0.3	0.87 (0.21-0.94)	<b>0.012*</b>	0.23±0.03	0.22 (0.19-0.26)	<b>0.009*</b>
	Control	0.88±0.01	0.88 (0.86-0.9)		0.73±0.01	0.74 (0.71-0.75)		0.66±0.02	0.66 (0.64-0.68)		0.19±0.02	0.19 (0.17-0.22)	
GP	Patient	1.23±0.12	1.23 (1.12-1.42)	<b>0.001*</b>	0.97±0.09	0.97 (0.88-1.11)	<b>0.001*</b>	0.73±0.27	0.8 (0.28-0.95)	<b>0.021*</b>	0.25±0.02	0.24 (0.23-0.28)	0.674
	Control	0.98±0.06	1.01 (0.86-1.02)		0.77±0.03	0.79 (0.72-0.8)		0.67±0.02	0.68 (0.64-0.69)		0.26±0.02	0.27 (0.22-0.27)	
NA	Patient	1.32±0.09	1.33 (1.18-1.43)	<b>0.006*</b>	1.1±0.08	1.13 (0.99-1.18)	<b>0.005*</b>	0.83±0.36	0.94 (0.19-1.06)	<b>0.046*</b>	0.2±0.02	0.19 (0.18-0.23)	0.834
	Control	1.05±0.06	1.04 (0.96-1.13)		0.87±0.05	0.87 (0.8-0.95)		0.78±0.05	0.77 (0.71-0.86)		0.21±0.01	0.21 (0.19-0.23)	
Thal	Patient	1.39±0.11	1.38 (1.26-1.56)	<b>0.002*</b>	1.07±0.09	1.07 (0.96-1.19)	<b>0.001*</b>	0.78±0.28	0.87 (0.3-1.01)	<b>0.016*</b>	0.35±0.01	0.3 (0.28-0.32)	0.462
	Control	1.18±0.05	1.16 (1.12-1.24)		0.88±0.05	0.87 (0.83-0.95)		0.73±0.05	0.72 (0.68-0.8)		0.32±0.01	0.32 (0.3-0.34)	
EC	Patient	1.14±0.03	1.15 (1.1-1.18)	<b>0.001*</b>	0.84±0.04	0.86 (0.78-0.87)	<b>0.001*</b>	0.62±0.16	0.71 (0.34-0.72)	<b>0.027*</b>	0.33±0.02	0.33 (0.31-0.37)	0.916
	Control	1.02±0.03	1.02 (0.97-1.05)		0.73±0.02	0.73 (0.71-0.76)		0.59±0.02	0.58 (0.57-0.62)		0.36±0.02	0.36 (0.33-0.39)	
AL	Patient	1.4±0.12	1.4 (1.23-1.54)	0.059	1.08±0.1	1.06 (0.96-1.2)	<b>0.046*</b>	0.77±0.29	0.87 (0.27-0.98)	0.294	0.29±0.03	0.3 (0.27-0.33)	0.834
	Control	1.27±0.11	1.29 (1.13-1.41)		0.96±0.1	0.94 (0.84-1.13)		0.81±0.1	0.77 (0.7-0.98)		0.31±0.04	0.31 (0.25-0.36)	
LF	Patient	1.5±0.12	1.54 (1.32-1.65)	0.345	1.03±0.12	1.04 (0.85-1.2)	0.141	0.72±0.21	0.79 (0.42-0.98)	0.345	0.41±0.04	0.42 (0.36-0.45)	0.600
	Control	1.48±0.11	1.49 (1.3-1.63)		0.98±0.09	1 (0.82-1.09)		0.73±0.08	0.75 (0.58-0.82)		0.43±0.02	0.43 (0.41-0.46)	

sd: standard deviation, M: Median, p: Mann Whitney U test significance value, \*p<0.05; there is a statistically significant difference between the groups. ALIC: Crus anterior capsula interna PLIC: Crus posterior capsula interna RLIC: Pars retrolentiformis Snigra: Substantia Nigra Caud: Nucleus Caudatus Put: Putamen GP: Globus Pallidus NA: Nucleus Accumbens Thal: Thalamus EC: Capsula Externa A: Ansa lenticularis LF: Fasciculus lenticularis

For AD; SLF ( $p=0.001$ ), IFO ( $p=0.001$ ), UNC ( $p=0.016$ ), SS ( $p=0.001$ ), ACR ( $p=0.001$ ), SCR ( $p=0.001$ ), PCR ( $p=0.002$ ). A statistical significant dissimilarity was found through the groups (patient and control) (Table 5). for MD; SLF ( $p=0.001$ ), IFO ( $p=0.001$ ), UNC ( $p=0.001$ ), SS ( $p=0.002$ ), ACR ( $p=0.001$ ), SCR ( $p=0.001$ ), PCR ( $p=0.001$ ). A statistical important dissimilarity was found through groups (patient and control) (Table 5). For RD; SLF ( $p=0.016$ ), IFO ( $p=0.012$ ), UNC ( $p=0.024$ ), SS ( $p=0.021$ ), ACR ( $p=0.012$ ), SCR ( $p=0.021$ ), PCR ( $p=0.046$ ) A statistically important dissimilarity was found through the groups (patient and control) (Table 5). No statistical important dissimilarity through the groups (patient and control) in FA measures ( $p>0.05$ ) (Table 5). For AD; ALIC ( $p=0.001$ ), PLIC ( $p=0.001$ ), RLIC ( $p=0.001$ ), Caud ( $p=0.001$ ), Put ( $p=0.001$ ), GP ( $p=0.001$ ), NA ( $p=0.006$ ), Thal ( $p=0.002$ ), EC ( $p=0.001$ ) measures were statistical significant dissimilarity through groups (patient and control) (Table 6). For MD; ALIC ( $p=0.001$ ), PLIC ( $p=0.001$ ), RLIC ( $p=0.001$ ), Caud ( $p=0.001$ ), Put ( $p=0.001$ ), GP ( $p=0.001$ ), NA ( $p=0.005$ ), Thal ( $p=0.001$ ), EC ( $p=0.001$ ), AL ( $p=0.046$ ) measures were statistical important dissimilarity through groups (patient and control) (Table 6). For RD; ALIC ( $p=0.003$ ), PLIC ( $p=0.012$ ), RLIC ( $p=0.027$ ), Caud ( $p=0.012$ ), Put ( $p=0.012$ ), GP ( $p=0.021$ ), NA ( $p=0.046$ ), Thal ( $p=0.016$ ), EC ( $p=0.027$ ) measurements were statistical significant dissimilarity through the groups (patient and control) (Table 6). For FA; A statistical significant dissimilarity was found through the groups (patient and control) in Caud ( $p=0.005$ ) and Put ( $p=0.009$ ) measurements (Table 6).

## DISCUSSION

White matter degeneration is important in the progression of HD. DTI is widely used to reveal white matter microstructural alterations related with HD pathology (22). Ciarmiello et al. explained that the degeneration of the brain in HD affects both subcortical and cortical regions (23). The reducing in white matter volume might affect the reduction in the number of axons in the impressed area and the reduction in the quantity of myelin surrounding the axons. They stated that there may be a decrease in white matter volume before gray matter atrophy and this is related to neuronal dysfunction. Zhang et al. showed that reduced axonal density is one of the main factors underlying pre-HD white matter pathology (10). Matsui et al. observed an increase in RD and FA worths in the prefrontal white matter tracts in HD (24). Klöppel et al. realized that a decrease in connectivity among the frontal cortex and truncus corporis callosi in PreHD compared to control (25). In our study, AD, MD, RD and FA worths were found to be increased in the capsula interna and capsula externa in the patient than the control group. Most studies showed that an increased FA and RD in capsula externa and capsula interna for HD, PreHD than healthy controls (11,22,2). In this study, AD, MD, RD and FA worths were determined to be increment in the patient group in the fasciculus longitudinalis superior and fasciculus longitudinalis inferior by comparison to the control group. Most studies noticed that a declined FA

and an increment MD, AD, RD in fasciculus longitudinalis superior and fasciculus longitudinalis inferior for HD, PreHD than healthy controls (10,11,22,26,27). Saba et al. stated that decrease in FA is an indicator of a degenerative process and axonal loss (11).

Harrington et al. found that some cognitive areas such as motor planning, verbal learning, memory, sensory-perceptual processing were affected (28). In our study, AD, MD, RD and FA worths were found to be increased in the sagittal stratum and cingulum in the patient group than control group. Most studies indicated that declined FA and increment MD in cingulum for HD, PreHD by comparison to healthy controls (22,26). In this study AD, MD, RD and FA worths were higher in the cingulum patient group than control group. Most studies showed that a declined FA in corona radiata for HD, PreHD by comparison to healthy controls (10,11,22). In our study, AD, MD, RD worths were found to be increased in the corpus callosum parts of the patient group than control group. Rosas et al. found a decrease in FA in the truncus corporis callosi, genu corporis callosi and splenium corporis callosi parts in the patient group by compared to controls (29). Rosas et al. proposed that an increment in RD and AD in fibers of corpus callosum (30). Mazerolle et al. stated that damage in the corpus callosum may affect the transfer of cognitive, sensory and motor knowledge among cortical areas (31). Matsui et al. found that increment FA and RD in the prefrontal white matter tracts in PreHD (24). Liu et al. explained that this showed the corpus callosum also showed demyelination as well as axonal degeneration in preHD (31). Most works indicated that a decline in FA and increment AD, MD, RD and in a corpus callosum regions for HD, PreHD than healthy controls (8-11,16,22,25). Subcortical nuclei had been extensively studied in those with HD. In our study, AD, MD, RD values in subcortical nuclei in the patient group increased than the control group. Most studies showed that an increased FA, MD in subcortical regions for HD, PreHD compared to healthy controls (6,7). In this study we found an increase in MD, RD and AD worths in the nucleus caudatus in the patient than the control group, and there was an increment in the FA worths and it was found to be significant. Rosas et al. indicated that a substantial difference in FA in the nuc caudatus in PreHD and HD patients (29). Novak et al. suggested that white matter microstructural alterations in individuals with HD were related with alterations in the volume of the nucleus caudatus (26). Most studies showed that an increased FA and decreased MD in nucleus caudatus for HD, PreHD than healthy controls (26,32). One study showed that a decline FA and increment MD in nucleus caudatus for HD, PreHD compared to healthy controls (3). In our study, we found an increment in AD, MD, RD, FA and worths in the corpus striatum in the patient group than the control group. Scientists showed that a decline in the FA worth in the corpus striatum and an increment in the MD value in the HD group than the healthy control group were found (9). Despite this, another study indicated that an increase in FA value in the corpus striatum in the HD group than



healthy control group (7). Multiple studies showed that an increased FA in globus pallidus for HD, PreHD than healthy controls (8,28,32). In our study, AD, MD, RD, FA worths were determined increment in the putamen and thalamus in the patient group than control group. Most studies showed an increased FA, MD in putamen, thalamus for HD, PreHD in comparison with healthy controls (7,8,29,32). Odish et al. noticed that the proportion of longitudinal spread alteration in gyrus occipitalis medius, gyrus occipitalis superior, and gyrus occipitalis inferior was substantially higher in the patient group compared to both preHD and controls. They interpreted this as an increasing proportion of microstructural degeneration (33).

In summary, when controls and HD were compared, MD and AD in frontal, parietal, temporal, occipital, corpus callosum, white matter, limbic and subcortical structures, RD in corpus callosum and capsular interna appear to be increased. The FA worths was higher in the nucleus caudatus and putamen and a significant difference was observed. It suggested dysmyelination in these regions. FA worths in the nucleus caudatus and putamen were significant and could be an indicator of a degenerative process, axon loss and inflammation in these regions.

### Limitations

The current study had some limitations, (1) the number of HD groups and control groups was small. The reason for this was that HD was a rare genetically inherited neurodegenerative disease and they did not want to have an MRI.

### CONCLUSION

We could not find a study in which all regions of the brain were examined in the literature review in studies using the DTI technique in Huntington's disease. Neurodegeneration is connected to the continuous and progressive loss of neurons that occurs in the structure of neurons. Early detection of neurodegeneration is very substantial for the improving of neuroprotective treatments for neurodegenerative illnesses in the future. Studies showed that myelin is an important neuropathological feature of neurodegenerative diseases. In conclusion, using the DTI technique, changes in diffusion parameters can be used as an alternative method to determine biomarkers of disease progression and the microstructural varies in HD. In addition, we believe that conducting studies on more patients to clarify the relationship among DTI measurements and clinical features will yield effective results on the course of the disease.

**Financial disclosures:** *The authors declared that this study has received no financial support.*

**Conflict of interest:** *The authors have no conflicts of interest to declare.*

**Ethical approval:** *The study was ratified by Erciyes University Faculty of Medicine Clinical Research Ethics Committee with protocol number 2019/643 (25.09.2019).*

### REFERENCES

1. MacDonald ME, Ambrose CM, Duyao MP, et al. Huntington Study Group. A novel gene containing a trinucleotide repeat that is expanded and unstable on Huntington's disease chromosomes. *Cell*. 1993;72:971-83.
2. Ross CA, Aylward EH, Wild EJ, et al. Huntington disease: natural history, biomarkers and prospects for therapeutics. *Nat Rev Neurol*. 2014;10:204-16.
3. Assaf Y, Pasternak O. Diffusion tensor imaging (DTI)-based white matter mapping in brain research: a review. *J Mol Neurosci*. 2008;34:51-61.
4. Sprengelmeyer R, Orth M, Muller HP, et al. The neuroanatomy of subthreshold depressive symptoms in Huntington's disease: a combined diffusion tensor imaging (DTI) and voxel-based morphometry (VBM) study. *Psychol Med*. 2014;44:1867-78.
5. Kurtoğlu E, Payas A, Düz S, et al. Analysis of changes in brain morphological structure of taekwondo athletes by diffusion tensor imaging. *J Chem Neuroanat*. 2023;129:102250.
6. Müller HP, Grön G, Sprengelmeyer R, et al. Evaluating multicenter DTI data in Huntington's disease on site specific effects: An ex post facto approach. *Neuroimage Clin*. 2013;32:161-7.
7. Douaud G, Behrens TE, Poupon C, et al. In vivo evidence for the selective subcortical degeneration in Huntington's disease. *NeuroImage*. 2009;46:958-66.
8. Andica C, Kamagata K, Hatano T, et al. MR biomarkers of degenerative brain disorders derived from diffusion imaging. *J Magn Reson Imaging*. 2020;52:1620-36.
9. Muhlau M, Weindl A, Wolschlagel AM, et al. Voxel-based morphometry indicates relative preservation of the limbic prefrontal cortex in early Huntington disease. *J Neural Transm*. 2007;114:367-72.
10. Zhang J, Gregory S, Scahill RI, et al. In vivo characterization of white matter pathology in pre-manifest Huntington's disease. *Ann Neurol*. 2018;84:497-504.
11. Saba RA, Yared JH, Doring TM, et al. Diffusion tensor imaging of brain white matter in Huntington gene mutation individuals. *Arq Neuropsiquiatr*. 2017;75:503-8.
12. Faul F, Erdfelder E, Buchner A, Lang AG. Statistical power analyses using G\*Power 3.1: tests for correlation and regression analyses. *Behavior Research Methods*. 2009;41:1149-60.
13. Mori S, Wu D, Ceritoglu C, et al. Mricloud: delivering high-throughput mri neuroinformatics as cloud-based software as a service. *Computing in Science & Engineering*. 2016;18:21-35.
14. Soysal H, Acer N, Özdemir M, et al. A volumetric study of the corpus callosum in the Turkish population. *J Neurol Surg B Skull Base*. 2021;83:443-50.
15. Turamanlar O, Kundakci YE, Saritas A, et al. Automatic segmentation of the cerebellum using volBrain software in normal paediatric population. *Int J Dev Neurosci*. 2023;83:323-32.
16. Ceritoglu C, Tang X, Chow M, et al. Computational analysis of LDDMM for brain mapping. *Front Neurosci*. 2013;7:15.

17. Tang X, Oishi K, Faria AV, et al. Bayesian parameter estimation and segmentation in the multi-atlas random orbit model. *PLoS One*. 2013;8:e65591.
18. Acer N, Kamaşak B, Karapınar B, et al. A comparison of automated segmentation and manual tracing of magnetic resonance imaging to quantify lateral ventricle volumes. *Erciyes Med J*. 2022;44:148-55.
19. Mukherjee P, Berman JI, Chung SW, et al. Diffusion tensor MR imaging and fiber tractography: theoretic underpinnings. *AJNR Am J Neuroradiol*. 2008;29:632-41.
20. Öz F, Acer N, Ceviz Y, et al. Volumetric analysis of the brain structures of children with Down's Syndrome: a 3D MRI study. *J Exp Clin Med*. 2021;38:197-203.
21. Yoshida S, Oishi K, Faria AV, et al. Diffusion tensor imaging of normal brain development. *Pediatr Radiol*. 2013;43:15-27.
22. Sweidan W, Bao F, Bozorgzad NS, et al. White and gray matter abnormalities in manifest Huntington's disease: cross-sectional and longitudinal analysis. *J Neuroimaging*. 2020;30:351-8.
23. Ciarmiello A, Cannella M, Lastoria S, et al. Brain white-matter volume loss and glucose hypometabolism precede the clinical symptoms of Huntington's disease. *J Nucl Med*. 2006;47:215-22.
24. Matsui JT, Vaidya JG, Johnson HJ, et al. Diffusion weighted imaging of prefrontal cortex in prodromal Huntington's disease. *Hum Brain Mapp*. 2014;35:1562-73.
25. Klöppel S, Draganski B, Golding CV, et al. White matter connections reflect changes in voluntary-guided saccades in pre-symptomatic Huntington's disease. *Brain*. 2008;13:196-204.
26. Novak MJU, Seunarine KK, Gibbard CR, et al. White matter integrity in premanifest and early Huntington's disease is related to caudate loss and disease progression. *Cortex*. 2014;52:98-112.
27. Di Carlo DT, Benedetto N, Duffau H, et al. Microsurgical anatomy of the sagittal stratum. *Acta Neurochirurgica*. 2019;161:2319-27.
28. Harrington DL, Smith MM, Zhang Y, et al. Cognitive domains that predict time to diagnosis in prodromal Huntington disease. *J Neurol Neurosurg Psychiatry*. 2012;83:612-9.
29. Rosas HD, Tuch DS, Hevelone ND, et al. Diffusion tensor imaging in presymptomatic and early Huntington's disease: Selective white matter pathology and its relationship to clinical measures. *Mov Disord*. 2006;21:1317-25.
30. Rosas HD, Lee SY, Bender AC, et al. Altered white matter microstructure in the corpus callosum in Huntington's disease: Implications for cortical "disconnection". *NeuroImage*. 2010;49:2995-3004.
31. Mazerolle E, D'Arcy RC, Beyea SD. Detecting functional magnetic resonance imaging activation in white matter: interhemispheric transfer across the corpus callosum. *BMC Neurosci*. 2008;9:84.
32. Liu W, Yang J, Burgunder J, et al. Diffusion imaging studies of Huntington's disease: a meta-analysis. *Parkinsonism & Related Disorders*, 2016;32:94-101.
33. Odish OFF, Reijntjes RHAM, van den Bogaard SJA, et al. Progressive microstructural changes of the occipital cortex in Huntington's disease. *Brain Imaging and Behavior*, 2018;12:1786-94.