



# Evaluation of Brain Diffusion Tensor Imaging Parameters and Effectivity in Children with Autism

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## ABSTRACT

**Objective:** To determine whether there were diffusion tensor imaging (DTI) changes [ADC (apparent diffusion coefficient), FA (fractional anisotropy), AD (axial diffusivity) ve RD (radial diffusivity)] between two cerebral hemispheres among children with autism in both right and left brainstems, association, projection, and commissural fibers and to compare these findings with those of normal healthy subjects.

**Methods:** Thirty children with autism and 16 age-matched healthy control subjects were included, and their Magnetic Resonance Imaging (MRI) and DTI findings were retrospectively evaluated.

**Results:** ADC values obtained from the right and left inferior fronto-occipital fasciculus were higher in the autistic subjects than in the control group. FA values obtained from the anterior limb of the right internal capsule, right external capsule, right inferior frontooccipital fasciculus, right corticospinal tractus, right forceps major, and genu of the corpus callosum were lower in the autistic subjects than in the control group. RD values obtained from the right cingulum were higher compared with those from the left cingulum. AD values obtained from the right and left forceps major were lower, and RD values obtained from the left forceps major were higher in the autistic subjects compared with the control group.

**Conclusion:** In subjects with autism, DTI parameter changes demonstrated in various brain regions, especially in the limbic system, may be attributed to the social and communication impairment in autism. DTI may be used as an assisting method in autism, which is a heterogeneous disease affecting many locations in the brain.

**Keywords:** Autism, diffusion tensor imaging, ADC, FA, RD

## Introduction

Autism spectrum disorders (ASD) include neurodevelopmental states characterized by recurrent and ordinary behaviors as well as impaired speech and social communication (1). The prevalence of ASD is 6/1000 in children (2).

There are studies showing that social and communicative disorders are related to abnormalities in limbic structures in cases with autism spectrum disorders (3, 4). Limbic system structures such as cingulate gyrus and orbitofrontal cortex contribute to the development of individuals' self-awareness and capacity to understand others' behavior (5, 6). Amygdala and hippocampus

are involved in the storage of memory related to emotional events, facial recognition and processing of visual cues (7). In this respect, it is thought that these regions play an important role on social, cognitive and effective functions in patients with ASD. In addition, there are a number of structural and functional neuroimaging studies showing that early social disorders of autism are associated with abnormalities detected in certain regions of the frontal lobe responsible for social-cognitive communication (8, 9).

In recent years, there are studies determining the presence of a number of disorders in the connection pathways such as

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**Received:** 24.05.2017  
**Accepted:** 23.10.2017

**Cite this article as:** Kurtcan S. Evaluation of Brain Diffusion Tensor Imaging Parameters and Effectivity in Children with Autism. Bezmialem Science 2018; 6(4): 283-7.

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association and commissural fibers that provide the connection in different lobes and hemispheres in the brains of patients with autism with advanced imaging techniques such as Diffusion Tensor Imaging (DTI) and functional MRI (10, 11). However, it is stated that there are some inconsistencies between screening protocols, processing of images and non-standardization of analysis methods and variations in the parameters used in the evaluation of cases and the imaging protocols in the literature related to heterogeneity (12). In our study, ADC (apparent diffusion coefficient), FA (fractional anisotropy), AD (axial diffusivity) and RD obtained from white matter tracts such as brain stem, projection, association and commissural fibers in both left and right sides of the brain (radial diffusivity) values in children with autism were used to determine whether there was any difference between the two groups and also to compare the findings with the healthy control group.

## Methods

The retrospective study included 30 patients (25 males and 5 females) with autism and 16 healthy controls (12 males, 4 females). The age range was 3-14 years in the autism group and 3-13 years in the healthy control group.

The control group was composed of normal healthy subjects who were admitted to the outpatient clinic and who did not have any features in their clinical histories and whose physical examination and MRI were reported as normal. Cranial MRI and DTG evaluation of patients with autism and healthy control group were retrospectively analyzed from the archives of the Department of Radiology of Bezmialem Vakif University. The study was approved by Bezmialem Vakif University Non-Interventional Clinical Research Ethics Committee (Date: 26.04.2017, No: 7583).

## Imaging method

Imaging was performed with 1.5-T MRI system using head coil (Siemens, Avanto, Erlangen, Germany). The routine MRI protocol was based on spin-echo T1-weighted (TR: 550 ms, TE: 20 ms; section thickness, 5 mm; FOV, 240x240 mm<sup>2</sup>; matrix, 125x256), T2-weighted (TR: 4530 ms, TE: 100 ms; cross-section thickness, 5 mm; FOV, 240x240 mm<sup>2</sup>; matrix, 211x384) and FLAIR (TR: 8000 ms, TE: 90 ms, TI: 2500 ms; section thickness, 5 mm; FOV, 240x240 mm<sup>2</sup>; matrix, 140x256) images.

DTG was obtained by applying 30 different diffusion sensitive gradient with 2 different b values ( $b = 0$  and  $b = 1000 \text{ s} / \text{mm}^2$ ) to the single-shot echo-planar sequence determined as TR / TE, 6000/89 ms; matrix, 128x128; FOV, 230x230 mm<sup>2</sup>; thickness section, 5 mm; spacing between sections, 1.5 mm; number of sections, 20; spatial resolution 1.54. The data obtained from the DTG were transferred to the Leonardo console (software version 2.0, Siemens) for further processing, and the DTG parameters (ADC, FA, AD, RD) were measured from the areas determined in the brain in both right and left sides. In the control group, the mean values of the DTG parameters measured from the right and left hemisphere were averaged.

## Region of interest (ROI) analysis

ADC, FA, AD and RD values were measured by using the ROI from corpus callosum genu and splenium from both the right and left sides of the localizations of cingulum, superior longitudinal fascicle, inferior fronto-occipital fasciculus, uncinate fasciculus, forceps minor and major, external capsule, anterior and posterior limb of internal capsule, cortico spinal tract from white matter tracts such as brain stem, projection, association, and commissural fibers determined in DTG taken after MRI performed to exclude organic brain disorder in cases with autism. ROIs were carefully hand-drawn in the size range ranging from 10 to 40 mm<sup>2</sup> depending on the size of the selected area (Figure 1).

## Statistical analysis

Statistical analysis was performed using the statistical package program (SPSS Inc.; Chicago, IL, USA). Mann-Whitney U test was used to compare ADC, FA, AD and RD values obtained from patients with autism and healthy control group. The level of significance was determined as  $p < 0.05$ .

## Results

When compared with the control group, ADC values obtained from the right and left inferior fronto-occipital fascicle ( $p = 0.03$ ) of the patients with autism were statistically significantly higher. FA values obtained from the right internal capsule anterior leg ( $p = 0.001$ ), right external capsule ( $p = 0.001$ ), right inferior fronto-occipital fasciculus ( $p = 0.001$ ), right corticospinal tractus ( $p = 0.001$ ), and right forceps major ( $p = 0.03$ ) and corpus callosum genu ( $p = 0.003$ ) were lower than control group.

RD values obtained from the right cingulum were statistically significantly higher than those obtained from the left cingulum ( $p = 0.011$ ). The AD values obtained from the right and left forceps major levels were lower than the control group ( $p = 0.048$ ,  $p = 0.046$ ). RD values obtained from the left forceps major level were higher than the control group ( $p = 0.030$ ) (Table 1). There was no statistically significant difference in DTG parameters obtained from other areas.

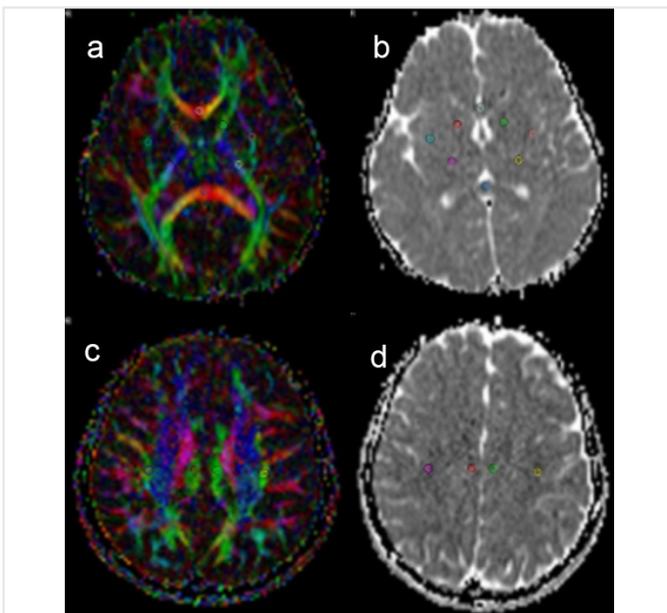
## Discussion

Diffusion Tensor Imaging is a method that can be used to assess the structural integration of white matter tracts in the brain and to describe pathological changes in the microstructural level, such as axonal or myelin damage. White matter integrity is evaluated by obtaining quantitative information about the direction and degree of diffusion of water in unit volume with DTG (13). While ADC, which is one of the DTG parameters, indicates the magnitude of diffusion of water molecules in tissue, FA reflects myelination, axonal diameter and fiber density in white matter (14, 15). While AD axonal fragmentation showing the direction of diffusion of water is affected by the deposition of filaments and the deterioration of microtubule arrangement and the expansion of the extracellular distance, RD, which is thought to reflect the diffusion vertical to the axonal bundles, is mainly affected by myelin in the white matter (16, 17).

**Table 1: FA, ADC, AD and RD values obtained from different areas of the brain in cases with autism and control group**

Localization	Autism	Control
	FA	FA
Right ICAL	0.45±0,09	0.59±0.12
Right EC	0.38±0,09	0.49±0.09
Right IFOF	0.52±0,07	0.63±0.09
Right CST	0.56±0,12	0.72±0.07
Right FM	0.61± 0.17	0.71±0.12
CC genu	0.76±0.09	0.83±0.05
	ADC (10 <sup>-3</sup> mm <sup>2</sup> /s)	ADC (10 <sup>-3</sup> mm <sup>2</sup> /s)
Right IFOF	0.90±0.07	0.84±0.09
Left IFOF	0.94±0.12	0.84±0.09
	AD (10 <sup>-3</sup> mm <sup>2</sup> /s)	AD (10 <sup>-3</sup> mm <sup>2</sup> /s)
Right FM	1.43±0.24	1.54±0.15
Left FM	1.40±0.22	1.54±0.15
	Autism RD (10 <sup>-3</sup> mm <sup>2</sup> /s)	Control RD (10 <sup>-3</sup> mm <sup>2</sup> /s)
Right cingulum	0.63±0.09	0.58±0.11
Left cingulum	0.53±0.12	0.58±0.11
Left FM	0.58±0.12	0.48±0.17

Values were given as mean ± standard deviation, ADC: apparent diffusion coefficient; FA: fractional anisotropy, AD: axial diffusivity, RD: radial diffusivity, ICAL : internal capsule anterior leg, EC: External capsule, IFOF: inferior fronto-occipital fascicle, CST: cortico spinal tract, FM: forceps majör, CC: Corpus callosum



**Figure 1. a-d.** The placement of ROIs in color FA and ADC mapping is shown in Diffusion Tensor Imaging. Internal capsule anterior and posterior leg external capsule, corpus callosum genu and splenium (a, b), cingulum and superior longitudinal fascicle (c, d)

The only fascicle that provides connection of all four major lobes in the brain, namely frontal, temporal, parietal and occipital lobe is the inferior fronto-occipital fasciculus (18). This fascicle plays an important role in connecting all components for the processing of social information commonly referred to as social brain. Therefore, in patients with autism spectrum disorder,

it is hypothesized that there are widespread disorders in long connection pathways with deviations in the inferior fronto-occipital fasciculus. The decrease in the FA values obtained from this pathway in the DTG studies supports this hypothesis (12). Jou et al. (12) reported that all major tracts were affected in their study, but the effect was not equal in all tracts.

They refer to the maximal number of voxally affected forceps minor as the affected tract, followed by the right and left inferior fronto-occipital fasciculus. They also report that the right inferior fronto-occipital fasciculus is more severely affected. In our study, we found increased ADC values in both right and left inferior fronto-occipital fasciculus of patients with autism and decreased FA values in right inferior fronto-occipital fasciculus. These bilateral findings may show microstructural changes such as loss of myelin in the patients with autism or disruption of fiber integration by dysmyelination.

Corpus callosum is also reported to be affected in patients with autism as a result of a decrease in the FA values detected in corpus callosum fibers in the literature (19). Kumar et al. (1) reported that they found decreased FA values in corpus callosum and right cingulum, uncinate fasciculus and arcuate fasciculus in patients with autism spectrum disorder. While Ogur et al. (11) reported decreased FA values in the corpus callosum genu and splenium, the largest axonal pathway in the brain, which continues the interhemispheric information flow in the brain, some studies have shown that especially anterior part of corpus callosum is affected and this may be as a result of damage in the prefrontal region (20). These findings suggest that the effects of corpus callosum may be related to social deficits, repetitive behaviors and sensory abnormalities.

In our study, decreased FA values in the right forceps major and corpus callosum genu in the patients with autism, decreased AD values in both the right and left forceps major level, and increased RD values in the left forceps major level were detected and RD values obtained from the right cingulum were higher than those in the left cingulum. Assis et al. (21) reported that they detected decreased FA in many long white matter tracts, in the whole corpus callosum, bilateral posterior thalamus, and optic tract, and they found increased RD values in these regions with increased MD values, in most association and projection fibers indicating their myelinization defect. They also did not find significant differences in AD values in these regions (21). In our study, decreased RD values with decreased FA and AD values, which are more prominent in right hemisphere, may show deterioration in axonal integration and organization by decreasing myelinization and axon numbers.

Kumar et al. (1) hypothesized that the corticospinal tract will not be affected in autism cases and reported that they investigated the control tract in their studies. However, there are studies in the literature indicating that the corticospinal tract is affected as a projection fiber tract (10, 12). In our study, we found decreased FA values in the right corticospinal tract and decreased FA values in the right external capsule as the projection tract. In our study, FA values of the right internal capsule anterior leg were lower than the control group. In the literature, Ogur et al. (11) found a negative correlation between FA values obtained from the anterior leg of right internal capsule and stereotypic behavior and lethargy in cases with autism. This supports the general view that the internal capsule is responsible for behavioral and intellectual symptoms.

The most important limitation of our study is the low number of cases with autism. Another important limitation was the fact that no evaluation was made in terms of whether there was a correlation between neurological findings and neuropsychiatric tests and DTI findings since it was a retrospective study.

## Conclusion

Changes in the DTI parameters detected in the different localizations of the brain in children with autism, especially in the limbic system structures may be related to the social and communicative disorders observed in autism. DTG can be used as a supportive method in the follow-up of autism, being a heterogeneous disease in which many different localizations are affected.

**Ethics Committee Approval:** Ethics committee approval was received for this study from the ethics committee of Bezmialem Vakif University (2017/7583).

**Informed Consent:** Written informed consent was obtained from patients who participated in this study.

**Peer-review:** Externally peer-reviewed.

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

**Financial Disclosure:** The author declared that this study has received no financial support.

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