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Original Article

Relation of behavior problems with findings of cranial diffusion tensor MRI and MR spectroscopy in autistic children

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Abstract: Purpose: To investigate any relation of behavior problems with cranial Diffusion Tensor Imaging (DTI) and Magnetic Resonance Spectroscopy (MRS) findings in autism spectrum disorders. Materials and Methods: A total of 20 males children (12 autistic patients and 8 healthy controls) was examined by cranial DTI and MRS. The Aberrant Behavior Checklist (ABC) was used to calculate the irritability, lethargy-social withdrawal, stereotypic behavior, hyperactivity, and speech disorder scores for each patient. The results of MRS and DTI were evaluated together with the ABC scores. Results: Fractional anisotropy (FA) values demonstrated significant decreases in the left frontoparietal white matter, anterior limb of the right internal capsule, and left middle cerebellar peduncle as the behavior problem scores elevated ($P < 0.05$). With the exception of social withdrawal, as the behavior problem scores increased, metabolite levels increased, as well. Conclusion: The positive correlation between the MRS findings, behavior problem scores, and metabolite levels suggests the presence of a dysfunction leading to hypo and hyper neuronal function in various locations. Reduced FA values in DTI and negative correlation of behavior problems with FA values in the contralateral hemisphere, may indicate reduced myelination and abnormal axonal organization.

Keywords: Diffusion tensor imaging, magnetic resonance spectroscopy, autism

Introduction

Autism spectrum disorders (ASD) is a neurodevelopmental disease group affecting 0.6-1% of the general population [1] and it is characterized by defects in the social relations and speech abilities accompanied by a limited, repating, and stereotypic behavior pattern (APA 2000). From its first description to date, many structural and functional brain imaging studies have been conducted on ASD to investigate both underlying pathophysiology and neuroanatomy. DTI allows the examination of brain microstructure, while MRS enable us to evaluate the neurochemical status *in vivo*.

Many of the MRS studies on ASD have shown diffuse and localized decline in metabolite levels [2]. When combined with the clinical profile, Ch/Cr ratio increases in the left hippocampus-amygdala show an association with speech disorder [3]. NAA/Cr shows a significant decrease in the anterior cingulate gyrus (ACG), with further decline in NAA/Cr ratio, as the social ability is reduced. NAA/Cr and social ability correlates in left dorsolateral prefrontal cortex, whereas metabolite levels and behavior characteristics exhibit no significant changes in right dorsolateral prefrontal cortex [4]. In ASD, neuronal dysfunction and abnormal functional activation have been shown to be related [5]. A relationship has been demonstrated between the abnormal MRS metabolite levels and the severity of the symptoms in the prefrontal region in Asperger patients [6] and in temporal lobes in autistic people [7].

DTI allows to describe the structure of target tissue via measuring the diffusion speed and direction of water molecules. In various pathologies, DTI can provide a quantitative measure of microstructural organizations sensitive to white matter changes such as fractional anisotropy (FA) [8]. A drop in FA value indicates dam-

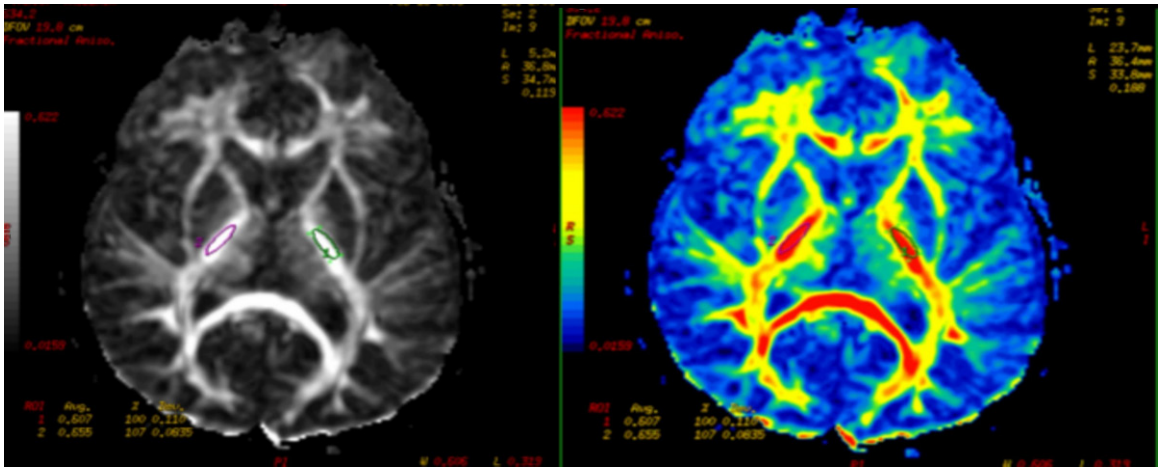

Figure 1. FA value and SD measurement via conventional ROI technique in the posterior limbs of the internal capsules in an autistic child.

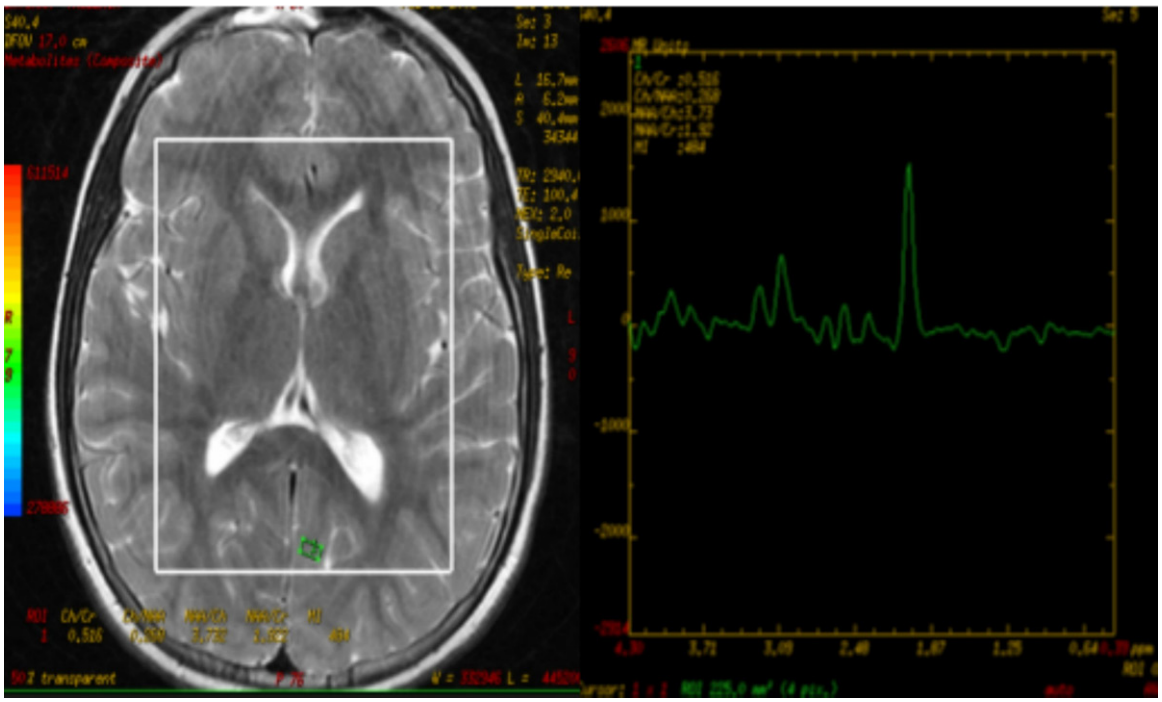

Figure 2. Ch/Cr, NAA/Ch and NAA/Cr ratios in the left occipital grey matter in an autistic child.

aged pathways leading to impaired axonal transport. ASD have been associated with low FA value in the corpus callosum (CC), and particularly in the anterior portion, by DTI studies [9]. The severity of the symptoms and the anterior 1/3 portion of the CC have been shown to be related [10]. Abnormal DTI parameters (elevated mean diffusion values) have been observed at the superior longitudinal fascicle level in relation with the speech disorders in ASD, with marked increases in the left cerebral hemisphere and temporal horn of the superior longitudinal fascicle [11]. Peeva and collegues showed the relationship of speech disorders and impaired pathway between left hemisphere ventral premotor cortex and supplementary motor area in high-functioning ASD [12]. The negative correlation between the FA values of

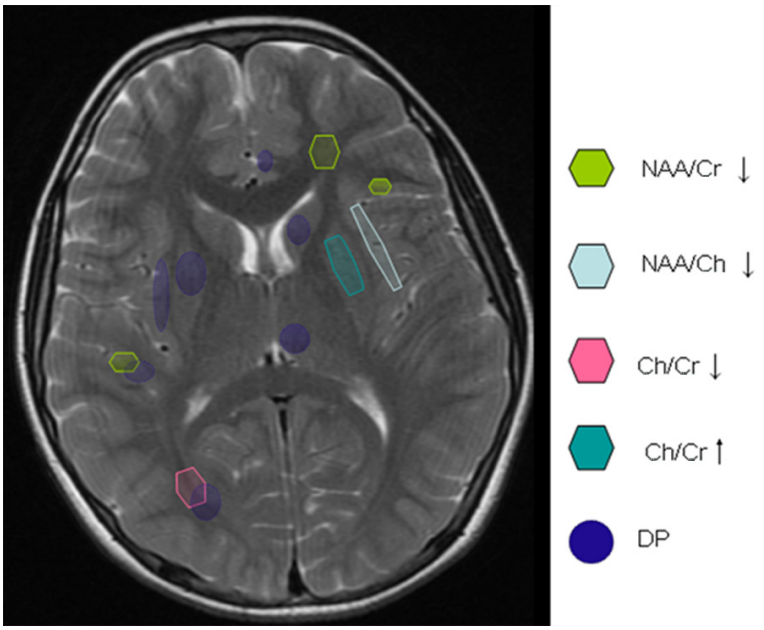

Figure 3. Statistically significant changes in metabolite concentrations in the autistic group are color-coded. The areas that metabolite changes correlated with the behavior problems (DP) have been shown were marked in circles/ellipsoids.

the affected fibers and the clinical symptom assessments of autism is known to be remarkable. In the light of these results, white matter microstructure hypothesis involving the frontotemporal cortical network associated with the disease symptoms in ASD can be regarded as confirmed [9].

Imaging studies possesses high importance for the effort towards explaining the mechanisms involving both neuroanatomy and pathophysiology of autism. In this study, we aimed to reveal the relationship of behavior problems with MRS and DTI studies.

Materials and methods

Patients

A total of 20 male children (12 autistic patients and 8 healthy controls) aged 3-15 years and with no diagnosis of any coexisting neurologic or psychiatric diseases were included in our study. 45 autistic children participated in the study. MRS and DTI of twenty autistic children could not be completed. MRS and DTI of thirteen autistic children have apparent motion artefacts and were removed from this study. The groups were assessed by Aberrant Behavior Checklist and Modified Checklist for Autism in Toddlers (M-CHAT) surveys, while both groups received DTI and MRS studies without applying any anesthetic agent. Classification according to age could not be performed due to limited number of participants.

Standard questionnaires and screening tests

Modified checklist for autism in toddlers: M-CHAT in Toddlers is a screening tool developed to detect early symptoms of autism or Pervasive Developmental Disorder (PDD) in children. M-CHAT has been developed as an extension of Checklist for Autism in Toddlers (CHAT). Although M-CHAT is a test for the children between 18 months and 36 months old, it is also used in children older than 36 months. It is not used younger than 18 months old children [13, 14]. By using M-CHAT in our study, we aim to determine the current status of autism patients who had been diagnosed previously.

Aberrant behavior checklist: This is a test aiming to determine the behavior problems in autistic children. Basically, it has been developed to reveal the behavior problems in handicapped people, however, it has also been observed to be an effective examination tool in neurogenetic diseases, mental retardation, and autism [15]. The ABC test has 5 subscales: Irritability, Lethargy-Social Withdrawal, Stereotypic Behavior, Hyperactivity, and Speech Disorder. The ABC test is filled out by the parents. The assessment is done based on the scores obtained from the subscales [15]. By using ABC in our study, we aimed to determine the current status of autism patients who had been diagnosed previously.

DTI

An MRI system of 1.5T General Electric SIGNA Excite (GE Medical Systems, Milwaukee, WI) was employed. Axial T1-, T2-weighted images and diffusion tensor sequences were applied.

Imaging was obtained in 25 directions by using 8-channel head coil and EPI sequence for DTI. The parameters of diffusion tensor were as follows: section thickness, 6mm; section interval, 1 mm; number of sections, 16; TE = 89 ms (minimum); TR = 6500 ms; FOV, 28 cm; number of excitations (NEX), 2; b = 1000 sn/mm^2; matrix, 160 × 128. The images were taken on the axial-oblique plane.

A total of 416 diffusion tensor images obtained from the study groups were transferred to the workstation (Advantage Workstation 4.1 GE Medical Systems). FA value was calculated via conventional region of interest (ROI) technique on axial images reflecting the anterior and posterior limbs of the internal capsules (IC) (**Figure 1**), temporoparietal white matter, frontoparietal white matter (FPWM), and middle cerebral peduncles (MCP).

MR spectroscopy

We obtained axial T2-weighted images with fast spin echo sequence. The section thickness was 5 mm; section interval, 1.5 mm; TR, 2950 ms; TE, 100 ms; FOV, 24 cm, number of excitations (NEX) 2; matrix 512 × 256; bandwidth, 22.73. These images were used to determine the neuroanatomic structures on the 1H-MRSI voxels after the analysis. Axial-oblique images were acquired at the basal ganglia plane with the following settings: TR/TE, 1000/135; matrix, 20 × 20; voxel thickness, 16 mm; FOV, 24 cm; and NEX, 1. MR spectroscopy images of the study groups were transferred to the workstation and sampling was performed from both of the hemispheres including the frontal white matter (FWM), inferior frontal gyrus, lentiform nucleus (LN), temporoparietal gyrus (TPG), occipital white and grey matter, insular cortex, ACG, caudate nucleus (CN), and medial thalamus. Ch/Cr, NAA/Ch, and NAA/Cr ratios were measured with TE 135 ms in all participants (**Figure 2**).

Statistical analysis

The study data were analyzed by using SPSS for Windows version 16.0 (Chicago, IL, USA). The results were expressed as frequency, standard deviation (SD), and percentage values. Relationship between variables were checked by Pearson correlation test. *P* value was accepted as significant when it is equal or below 0.05.

Results

Neuropsychiatric tests

We calculated irritability, lethargy-social withdrawal, stereotypic behavior, hyperactivity, and speech disorder scores via Aberrant ABC test. Mean values of scores for irritability, lethargy-social withdrawal, stereotypic behavior, hyperactivity, and speech disorder for ABC test in autistic children are 10.72 ± 8.82, 9.90 ± 6.99, 6.45 ± 4.71, 17.00 ± 7.48 and 2.36 ± 2.01 respectively. Diagnosis accuracy increases as scores increase. The diagnoses of autism among the participants were confirmed by the M-CHAT test used in our study, as well. The mean value ± SD was 5.90 ± 1.30 for the 7 critical items, whereas it was 14.36 ± 3.38 for the 23 items.

MR spectroscopy findings and behavior problems

Multivoxel spectroscopy (TE: 135 msn) was used in order to determine Ch/Cr, NAA/Ch and NAA/Cr metabolite ratios (**Figure 1**). The mean absolute metabolite values as well as the minimal and maximal results were compared between the patient and control groups.

Ch/Cr ratio showed a decrease in the right occipital white matter (OWM) and an increase in the left LN. NAA/Ch exhibited a decline in the left insular cortex. Also, NAA/Cr ratio showed a decrease in the right TPG, left frontal white matter, and inferior frontal gyrus ($P < 0.05$).

We calculated irritability, lethargy/social withdrawal, stereotypic behavior, hyperactivity, and speech disorder scores of each patient by using ABC test while the correlations between those scores and the MR spectroscopy findings were investigated by Pearson's correlation test.

Each behavior problem had corresponding findings- in the left CN in autistic children. Accordingly, NAA/Cr showed a decrease while sterotypic behavior ($P = 0.006$; pearson correlation coefficient (r) = -0.828), hyperactivity ($P = 0.027$; $r = -0.828$) , and irritability scores ($P = 0.029$; $r = -0.719$) increase; increase in speech disorder showed a mild decrease in Ch/Cr ($P = 0.045$; $r = -0.677$); and NAA/Cr ($P = 0.005$; $r = -0.833$); and increase in lethargy/social withdrawal scores displayed a mild decrease in NAA/Cr ratio ($P = 0.004$; $r = -0.845$). The

Table 1. Relation of FA values obtained by conventional ROI technique in the patient and control groups

		Control Group (n = 8)		Patient Group (n = 12)			
	Mean ± SD	Minimum	Maximum	Mean ± SD	Minimum	Maximum	P değeri
CCG	0.60838 ± 0.086221	0.450	0.694	0.51775 ± 0.095231	0.372	0.683	*0.045**
CCS	0.72012 ± 0,058862	0,620	0.828	0.54358 ± 0.107038	0.394	0.772	*0.002**
R AIC	0.45875 ± 0,031707	0,428	0.524	0.38817 ± 0.075291	0.288	0.547	*0.011**
R PIC	0.64688 ± 0,035938	0,607	0,688	0.56858 ± 0.082265	0.463	0,694	0.054
L AIC	0.46900 ± 0.033726	0.426	0.519	0.37942 ± 0.084887	0.286	0.572	*0.012**
L PIC	0.66638 ± 0.040872	0.606	0.728	0.54833 ± 0.065475	0.414	0.655	*0.001**
R FPWM	0.43588 ± 0.044315	0.367	0.498	0.32600 ± 0.050494	0.259	0.438	*0.001**
L FPWM	0.38588 ± 0.058747	0.324	0.494	0.35450 ± 0.046915	0.280	0.445	0.316
R TPWM	0.40225 ± 0.075179	0.325	0.544	0.36717 ± 0.086619	0.268	0.518	0.487
L TPWM	0,39975 ± 0.072944	0.326	0.530	0.36517 ± 0.115925	0.165	0.544	0.537
R MCP	0.60525 ± 0.073895	0.455	0.689	0.49567 ± 0.100147	0.344	0.673	*0.025**
L MCP	0.64525 ± 0.078556	0.494	0.749	0.52850 ± 0.121773	0.326	0.675	*0.037**
TOTAL DTI	0.23225 ± 0.019710	0.216	0.279	0.24042 ± 0.046915	0.173	0.327	0.758

(CCG: Corpus callosum genu, CCS: Corpus callosum splenium, R AIC: Right anterior limbs of the internal capsule, R PIC: Right posterior limbs of the internal capsule, L AIC: Left anterior limbs of the internal capsule, L PIC: Left posterior limbs of the internal capsule, R FPWM: Right frontoparietal white matter, L FPWM: Left frontoparietal white matter, R TPWM: Right temporoparietal white matter, L TPWM: Left temporoparietal white matter, R MCP: Right middle cerebellar peduncle, L MCP: Left middle cerebellar peduncle).

increasing speech disorder score was associated with raised total NAA/Ch (P = 0.022; r = 0.741); and total NAA/Cr ratios (P = 0.014; r = 0.774) in the right hemisphere, raised NAA/Ch in the right LN (P = 0.021; r = 0.712) and right OWM (P = 0.008; r = 0.808), and raised NAA/Cr in the right TPG (P = 0.016; r = 0.730) and right insular cortex (P = 0.024; r = 0.702).

Increased hyperactivity score was negatively correlated with NAA/Cr ratios in the left CN (P = 0.027; r = -0.724), and there are positive correlations between increased hyperactivity and right hemisphere (P = 0.015; r = 0.769) and right OWM (P = 0.02; r = 0.750).

Raised irritability score was correlated with increased NAA/Cr ratio in the right OWM (P = 0.039; r = 0.692), while it is negatively correlated with left CN (P = 0.029; r = -0.719).

Increased stereotypic behavior score showed a negative correlation with the NAA/Ch ratio in the right TPG (P = 0.029; r = -0.719), positive correlation with the NAA/Ch ratio in the left medial thalamus (P = 0.026; r = 0.693), and negative correlation with the NAA/Cr ratio in the left CN (P = 0.006; r = -0.828).

Raised lethargy/social withdrawal score was associated with decreased Ch/Cr ratio in the left ACG (P = 0.037; r = -0.696) and low NAA/Cr ratio in the left CN (P = 0.004; r = -0.845) (**Figure 3**).

DTI findings and behavior problems

FA values were measured in patient and control groups by conventional ROI technique. In the ASD, FA values were low in the CC genu and splenium, anterior limb of both ICs and posterior limb of left IC, right FPWM, and both MCPs (P < 0.05) (**Table 1**).

Pearson's correlation was applied between the ABC test results and FA values. FA value in the left FPWM showed a negative correlation with the stereotypic behavior, lethargy/social withdrawal, hyperactivity, and irritability scores. Moreover, stereotypic behavior and lethargy/social withdrawal scores were observed to have a negative correlation with FA value in the anterior limb of the right IC, whereas hyperactivity score showed a negative correlation with the FA value in the left MCP (**Table 2**).

Discussion

ABC and M-CHAT which are neuropsychiatric tests were used in order to confirm autism diagnosis and in order to score their behavior problems in relation with the MRS and DTI findings.

Table 2. Relation of DTI results in various regions with Aberrant ABC scores (Pearson's correlation) irritability, lethargy/social withdrawal, stereotypic behavior, hyperactivity, and speech disorder scores

		TOTAL DTI	CC G	CC S	R AIC	R PIC	L AIC	L PIC	R FPWM	L FPWM	R TPWM	L TPWM	R MCP	L MCP
Total Score	r*	,104	-,470	-,437	-,641*	-,045	-,064	,181	,243	-,809**	-,384	-,529	,141	-,571
	p	,762	,144	,179	,034	,895	,853	,593	,471	,003	,244	,095	,679	,066
Irritability	r*	,274	-,418	-,519	-,554	-,169	,033	,035	,065	-,854**	-,352	-,599	,268	-,570
	p	,416	,201	,102	,077	,619	,923	,919	,850	,001	,289	,051	,425	,067
Lethargy/social withdrawal	r*	-,038	-,413	-,377	-,700*	,039	-,425	,156	,496	-,642*	-,271	-,323	-,018	-,523
	p	,913	,207	,253	,016	,909	,193	,647	,121	,033	,421	,333	,958	,099
Stereotypic behavior	r*	,098	-,490	-,596	-,626*	-,139	-,309	-,094	,232	-,812**	-,265	-,434	,139	-,519
	p	,774	,126	,053	,039	,683	,355	,784	,492	,002	,430	,182	,683	,102
Hyperactivity	r*	,128	-,443	-,212	-,417	-,023	,299	,351	,213	-,658*	-,432	-,495	-,019	-,602*
	p	,707	,172	,532	,202	,946	,372	,290	,529	,028	,185	,122	,956	,050
Speech disorder	r*	-,397	-,128	,013	-,551	,415	,133	,610*	-,179	-,342	-,348	-,378	,517	,260
	p	,226	,707	,969	,079	,204	,696	,046	,599	,303	,295	,252	,103	,441

*r = Pearson correlation coefficient. (CCG: Corpus callosum genu, CCS: Corpus callosum splenium, R AIC: Right anterior limbs of the internal capsule, R PIC: Right posterior limbs of the internal capsule, L AIC: Left anterior limbs of the internal capsule, L PIC: Left posterior limbs of the internal capsule, R FPWM: Right frontoparietal white matter, L FPWM:Left frontoparietal white matter, R TPWM: Right temporoparietal white matter, L TPWM: Left temporoparietal white matter, R MCP: Right middle cerebellar peduncle, L MCP: Left middle cerebellar peduncle).

In this study, MRS imaging showed significant decreases in overall metabolite levels in the ASD. Regarding the MRS findings and autistic behavior characteristics, there was a positive correlation between the metabolite levels and behavior problem scores, suggesting a neuronal dysfunction leading to hypo and hyper functionality in different localizations. As proposed by Baron-Cohen and colleaques in 1999, autistic people appear to suffer from an inability to activate the proper cerebral areas responsible for language and social cognitive skills in the brain, while they try to activate other cerebral areas in order to perform the same activities [16].

NAA level, regarded as a neuronal marker that reflects neuronal density and viability or NAA/Cr ratio, displayed a decline in various cerebral areas, particularly frontal lobe, in the ASD [2, 3]. Lethargy-social withdrawal score exhibited a negative correlation with the Ch/Cr ratio in the left ACG. There is a growing mass of evidence indicating a relationship between autism, and functional and structural ACG abnormalities [2]. Asperger syndrome has shown a correlation between raised prefrontal NAA and obsessive behaviors, and between raised prefrontal cholin level and reduced social functions [6]. Dysfunction of the ACC, and medial prefrontal cortex have been associated with impaired social skills and reduced interpersonal communication [17], which is a finding supportive of our results.

In this study, as the stereotypic behavior score increased, NAA/Ch ratio decreased in the right TPG, NAA/Ch ratio increased in the left medial thalamus, and NAA/Cr decreased in the left CN. Previous studies have shown a link between increased CN size and stereotypic behaviors [18], moreover, the CN head has been reported to enlarge with aging in autistic childs, while declining in size in healthy controls [19]. In the present study, the relation of metabolite rates in the caudate and thalamus with stereotypic behavior score indicates the basal ganglia dysfunction in autistic children with stereotypic behavior.

Insula is one of the first locations that comes to mind when investigating the physiopathology of ASDs. Functional MRI studies show that dysfunctional anterior insula is strongly correlated with autism and has an important role in autism [20]. Moreover, insula hypoactivation has been reported in relation with social activities [21]. In healthy individuals, right anterior insula is activated during the vocal repeating of nonlyrical melodies, as speaking clearly requires left anterior insula [22]. However, in our study, autistic children showed a statistically significant decline in NAA/Ch ratio in the left insular cortex, while the aggravation of speech disorder was observed to be associated with rising NAA/Cr ratio in the right insular cortex when it was taken into account with ABC test metabolite ratios together.

Currently, it is a recognized fact that there is a link between speech center and brain laterality. In addition to arcuate fascicle, left thalamus and left CN take a role in speech, as well. In the present study, as the speech disorder score rose the left CN, Ch/Cr and NAA/Cr ratios decreased. Otherwise, as the speech disorder score increased, NAA/Ch and NAA/Cr increased in the right hemisphere, as well. Moreover, speech disorder score showed a positive correlation with NAA/Cr ratio in the right LN, right insular cortex, and right TPG, as well as with NAA/Ch ratio in the right OWM. Planum temporale, located superior to the temporal lobe and recognized as one of the leading evidences of cerebral laterality, is normally expected to be asymmetrically large in the hemisphere containing the speech center, however, studies have not shown such a finding. Rojas and colleaques showed that left hemisphere and planum temporale on the left hemisphere were smaller than normal in autistic patients [23]. In the present study, as the speech problem aggravated, most of significant changes in cerebral metabolite levels took place in the right hemisphere which was a finding supporting the results of Rojas et al and suggesting neuronal dysfunction.

In our study, DTI was performed in 25 encoding directions by using EPI sequence. Ni and colleagues found no significant differences between 21 and 31 directions protocols for FA and mean diffusivity in ROI-based analysis [24]. Structural brain imaging studies have revealed many anatomic changes in autistic patients, indicating an extensive disorder in the neuron network during the early development period [25]. Cranial DTI showed low FA values reflect-

ing reduced myelination in nerve pathways, decreased axonal density, and impaired axonal integrity and organization [24, 26, 27].

CC, the widest axonal pathway of the brain maintaining the interhemispheric information flow in mammals, has been a focus of first DTI and volumetric studies in children with ASD [9, 26]. In the present study, DTI demonstrated low FA values in the CC genu and splenium. DTI studies have shown low FA values in CC subunits particularly in the anterior CC [9, 28]. Low FA value in the splenium may be resulted from a local damage in the cortical neurons or axons, whereas low FA in the genu may be a result of the same local damage in the prefrontal region. Although a group of authors conducted a study on children and adolescents with ASD, and found high FA values in the CC [27, 29]. Studies particularly focus on the rostral and genu subunits which connect prefrontal region to each other which is the most frequently suggested as responsible area for autism. The severity of the symptoms and CC anterior 1/3 segment are associated [10] and the reduced volume in CC subunits may be related to social deficit, repeating behaviors, and sensory abnormalities which is explained by reduced interhemispheric connections and establishment of aberrant connection [30].

As compared to the healthy individuals, our participants exhibited low FA values in the anterior limb of both ICs and in the posterior limb of left IC. The low FA value in the anterior limb of both ICs reflects a problem in the bilateral thalamus-frontal connection or bilateral thalamus-ACG connection. On the other hand, posterior limb of the IC is the transit point of most of the motor pathways including the ones that reach spinal cord and it may be accepted as responsible for many abnormalities in autism [26]. Some studies in autistic patients have revealed low FA values in the posterior [31] and retrolenticular [28] parts of the right IC, posterior limb of both ICs [32], and all segments of the both ICs [26]. A study on stroke showed that NAA loss in the IC was associated with motor deficit [33]. In the present study, FA value in the anterior limb of the right IC demonstrated a negative correlation with the stereotypic behavior and lethargy/social withdrawal scores. In general, damage in the IC is believed to be responsible for the behavioral and intellectual symptoms which is supported by the results of our study, as well.

In our study, right FPWM showed significantly low FA values. When considered with the ABC test, FA value in the left FPWM displayed a negative correlation with the stereotypic behavior, lethargy/social withdrawal, hyperactivity, and irritability scores in autistic children. Social behavior problems are related to the social cognitive network in which frontal lobe has an important role and they emerge as the first symptoms of autism [16]. In the present study, right hemisphere showed significant decreases in FA, while the left hemisphere demonstrated a significant decline in FA values negatively correlated with behavior problems in ASD; these findings are suggestive of the abnormal axonal organization and reduced myelination proposed by Cascio and colleqgues [34].

MCP is the widest peduncle and can take a copy each of the motor stimulation commands delivered from the pyramidal tract to lower motor neurons. We determined significantly low FA values in both MCPs. Other studies in the literature showed reduced [26] and increased [31] FA values in both MCPs. Some recent studies have considered inadequate communication between cerebellum and other parts of the brain as the cause of motor dysfunction in ASD [35]. Hanaie and colleagues showed a possible correlation between low FA value in the right superior cerebellar peduncle and motor dysfunction in ASD [35]. In the present study, hyperactivity score displayed a negative correlation with the FA value in the left MCP.

Our study has some limitations, and the low number of participants in the same age for patient and control groups was the evident limitation of our study. The most important reason behind this fewness of participants was performing DTI without using anesthetics. Because we used ROI technique for DTI, the measurements could be performed manually on predetermined areas, comparisons were limited only to the FA values, and revealing morphologic characteristics such as the longevity and thickness of the pathways were other limitations of our study. The other limitation of our study is 6 mm section thickness that may cause an increase in partial volume artifacts in all diffusivity measures in DTI. Also, when evaluating DTI and MRS, the absence of a comparison between them, by designing MRS measurements based on the pathway localization in

DTI, may be considered as another limitation in our study.

Conclusion

The neurobiology and neuropathology of autism, a multisystemic disease with marked involvement of the central nervous system, is not understand clearly. In our study, reduced metabolite levels shown by MRS in the autistic group which has been reported in the literature, as well. In this study, MRS findings and the positive and negative correlation (especially caudat nucleus of the contralateral hemisphere) between behavior problem scores and the metabolite levels suggest a dysfunction leading to hypo and hyper functioning of the neurons in various localizations. In our study, getting reduced FA values in DTI, while, behavior problems exhibiting a negative correlation with the contralateral hemisphere may indicate abnormal axonal organization and reduced myelination. The diffuse nature of the DTI and MRS findings show that autism is an heterogeneous disease affecting many locations in the brain at the supratentorial and infratentorial level rather than local areas.

Disclosure of conflict of interest

None.

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