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Brain volumetric and white matter structural connectivity alterations in autistic children: case–control study

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Abstract

Background Autism spectrum disorder (ASD) is a neurodevelopmental disorder that includes a large heterogeneous constellation of disorders with overlapping symptoms and clinical features. The diagnosis is based mainly on clinical symptoms meeting DSM-5 criteria with no radiologic or laboratory diagnostic investigations available yet. The specific neuropathologic aberrations occurring in ASD are still under investigation. This study aimed at providing a preliminary database for better understanding of the neuropathologic aspects of ASD, regarding both macrostructure and microstructure of the brain using magnetic resonance imaging. This case–control study included total of 40 children, 20 cases (diagnosed with ASD) and 20 control (Typically Developing Children, TDC) aged 2–18 years. 3D-T1 and Diffusion Tensor Images (DTI) were acquired. 3D-T1 images were uploaded to Volbrain and brain segmentation was done using Volbrain 2.0 pipeline. DTI data were analyzed using FSL where Tract-Based Spatial Statistics analysis was carried out and mean fractional anisotropy values obtained. Independent samples t test was used to compare means of both groups.

Results ASD group displayed statistically significant larger intracranial cavity, brain, white matter, grey matter and cerebrospinal fluid volumes ($p < 0.001$ for all except CSF volume $p = 0.01$) with the white matter occupying higher percentage of intracranial volume in ASD compared to TDC group ($p < 0.001$). The cortical thickness showed statistically significant larger volume in entorhinal cortex in ASD group compared to TDC group at both sides ($p < 0.001$ at right side, $p = 0.003$ at left side). Widespread statistically significant ($p < 0.001$) higher mean FA value was observed at multiple white matter tracts.

Conclusion These findings suggest that the main pathology of ASD is within the white matter. It also supports the hypothesis that autistic brain undergoes period of precocious growth in early years of life. Further studies with age and clinical severity stratification are needed to investigate temporal changes and severity related macrostructure and microstructure changes in autistic brains.

Keywords Autism spectrum disorder, Diffusion tensor imaging, Cerebral cortex thickness

Background

Autism spectrum disorder (ASD), a neurodevelopmental disorder, defined by social communication impairments with restricted/repetitive patterns of behaviors and interests [14]. It occurs early in life, typically developing within the first three years, yet its symptoms will not fully manifest until the demands surpass the individual's skill level [35]. It shows increasing prevalence, which doubled in less than a decade, mainly due to improved detection

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and growing awareness [20]. In Africa, prevalence of ASD was estimated to be 1.2% [18].

Because of the early onset of ASD in childhood, its life-long impact on social integration, health, quality of life and economic well-being of the affected individuals and their families is enormous, together with added direct and indirect costs to the educational, healthcare, and economic sectors. These causes emphasize the need to continue searching for enhanced detection methods, effective and targeted interventions and ultimately prevention [33].

Regarding neuroimaging, children with ASD exhibit widespread alterations in grey matter and white matter of the brain which may impact the development of brain networks that support receptive and expressive language [21]. Numerous findings of atypical connectivity and activity of social brain networks were detected, supporting that social communication impairment is among the core diagnostic features of ASD [33]. However, the specific neuropathologic aberrations occurring in ASD are yet to be determined, with multiple studies of functional connectivity demonstrated both functional hyper- and hypo-connectivity in children with ASD. [30].

Also for cortical thickness, magnetic resonance imaging (MRI) measurements are thought to reflect underlying microstructure of the cerebral cortex, including number and organization of the cortical neurons, and to some extent the adjacent white matter maturation [6], yet no consensus view on developmental causes and neuroimaging findings has emerged till now [33].

This lack of agreement among different studies regarding the structural and white matter connectivity abnormalities in ASD patient, and lack of published studies done in Egypt to the best of our knowledge, were the main motives to start this study aiming at providing a preliminary database for better understanding of the neuropathologic aspects of ASD using MRI.

Methods

Type of study and sampling

This is a case–control study that was conducted over the period from January 2020 to January 2022. Convenient sampling was used to recruit patients diagnosed with ASD from the neuropsychiatry outpatient clinic during this period, twenty patients were included. Twenty age- and sex-matched typically developing children (TDC) were recruited from the radiology department. Inclusion criteria were as follows: age > 2 years and < 18 years, clinical diagnosis of ASD, controls who are typically developing children, aged > 2 and < 18 years with no current or first-degree family history of developmental delay. Exclusion criteria were as follows: structural brain abnormalities on routine magnetic resonance imaging, known genetic conditions, other concomitant psychiatric or neurologic disorder, and metal implants.

Approval of research ethics committee and informed consent were obtained from all participants' guardians in this study. Privacy and confidentiality of all patient's data were guaranteed. All provided data were monitored and used for scientific purpose only.

All the included subjects were subjected to the following:

Clinical assessment

Psychological assessment of the children suffering autism spectrum disorder by a specialist psychiatrist as follows: ASD diagnosis was determined according to DSM-V [5] criteria based on developmental history and clinical interview. The autism severity and social maturity of the children were assessed by the Childhood Autism Rating Scale (CARS) [42]. This scale evaluates behavior in 14 domains that are affected by ASD, plus one parameter of the general impression of autism. The 14 domains are as follows: (a) relating to people,(b) imitation, social-emotional understanding; (c) emotional response, emotional expression, and regulation of emotions; (d) body use; (e) object use, object use in play; (f) adaptation to change, adaptation to change/restricted interests; (g) visual response; (h) listening response; (i) taste, smell, and touch response and use; (j) fear or nervousness, fear or anxiety; (k) verbal communication; (l) nonverbal communication; (m) activity level, thinking/cognitive integration skills; and (n) level and consistency of intellectual response. Scores between 1 and 4 are given for each domain: (1) indicates normal behavior appropriate for age level (no signs of autism), while (4) indicates a severe deviance with respect to the normal behavior (severe symptoms of autism). The scores for the single items are added together into a total score. The maximum CARS score is 60, and the cutoff for autism is 30. A total score between 15 and 29.5 is considered non-autistic. Scores of 30.5–37 rated as mildly–moderately autistic, while scores above 37.5 rated as severely autistic [42]. The CARS is a well-established scale for the screening and classification of childhood autism with good agreement with DSM-5 [4] diagnostic criteria. The internal consistency reliability alpha coefficient is 0.94, the interrater reliability correlation coefficient is 0.71, and the test–retest correlation coefficient is 0.88. CARS is appropriate for use with any child over 2 years of age.

MRI technique

MR imaging was performed using 1.5 Tesla MR Scanner (Philips Medical Systems, Achieva), with a circular polarized head-array coil. Sedation using oral chloral hydrate was used with non-cooperative subjects with

dosage of 25–50 mg/kg. Participants were required to lie in the supine position with their head securely fixed by a belt and foam pads to minimize head motion. Structural T1-weighted High-Resolution (HR) 3D MRI sequence was acquired in the oblique plane with the following parameters: TR 8.5 ms, TE 6 ms, Flip angles 15°, 1.2 mm thick, 0 mm gap, 1 NEX, FOV 22 cm, and a 256×192 matrix. Then Diffusion Tensor Imaging (DTI) protocol was obtained as follows: Repetition time msec/echo time msec, 8000/minimum; 24 diffusion directions; two excitations; b value, 1000 s/mm^2; two T2-weighted images; acquisition matrix, 112×112; field of view, 224×224 mm; section thickness, 2.0 mm; 0-mm gap; 64 sections.

Image analysis and outcome measures

MRI images were viewed by senior radiologist (20-year experience) for any structural abnormalities or motion artifacts that will degrade the semiautomated processing of the study. Automated image processing was then carried out by junior radiologist (8-year experience) using the following steps: Conversion of DICOM images to NIFTI format using MRIcon program [39] to be able to process them. For DTI analysis, voxel-wise statistical analysis of the FA data was done using TBSS (Tract-Based Spatial Statistics, [45], part of FSL [44]. First, fractional anisotropy (FA) images were created by fitting a tensor model to the raw diffusion data using FDT, then brain-extracted using BET [43]. All subjects' FA data were then aligned into a common space using the nonlinear registration tool FNIRT [2, 3], which uses a b-spline representation of the registration warp field. Next, the mean FA image was created and thinned to create a mean FA skeleton which represents the centers of all tracts common to the group. Each subject's aligned FA data was then projected onto this skeleton and the resulting data fed into voxel-wise cross-subject statistics.

3D-T1 images were uploaded to Volbrain which is an online automated MRI brain volumetry system, where intracranial extraction, brain tissue classification, brain macrostructure segmentation and subcortical structure segmentation were done using the volbrain 2.0 pipeline [26]. Then comparison between the values obtained in both groups was carried out.

In addition to total brain volume measurements obtained, the mirror neuron system component (opercular inferior frontal gyrus, precentral gyrus, supplementary motor area, angular gyrus, supramarginal gyrus and occipital lobe), social brain components (superior, middle and inferior temporal gyri, fusiform gyrus, temporal pole, entorhineal area, parahippocampal gyrus, medial frontal cortex, anterior cingulate cortex and amygdala) and repetitive restricted behavior brain components (caudate nucleus and orbito-frontal cortex) volumetry, cortical thickness and FA measurements were assessed.

Statistical analysis

Data were analyzed using IBM SPSS software package version 20.0. Student t test was used to test significance of difference between 2 means. Quantitative data were expressed as means ± SD, while qualitative data were expressed as numbers and percentages. A probability value (p value) < 0.05 was considered statistically significant.

Results

This case–control study was conducted on 40 children, grouped into two groups, with 20 subjects each, TDC group included 12 males and 8 females with mean age of 7.9 years, and ASD group with 14 male and 6 females with mean age of 7.5 years and mean CARS score of 40 (Table 1).

For brain macrostructural changes' assessment with volumetry, intracranial cavity, brain, white matter, grey matter and cerebrospinal fluid mean volumes showed statistically significant larger size in ASD group compared to TDC group (Table 2).

When comparing different brain regions (cerebral hemispheres, cerebellar hemispheres, vermis and brain stem) and cerebral lobes (frontal, parietal, temporal and occipital lobes) mean volumes, statistically significant larger size was found in ASD group ($p < 0.001$) (Table 3).

The mean percentage of total white matter, left cerebral, total cerebellar, right and left cerebellar white matter volumes showed statistically significant higher values in ASD group compared to TDC group (Table 4). At the same time, different grey matter components (cortical, subcortical and cerebellar) appear reduced in ASD group in comparison with TDC group (Table 5). This reduction is statistically significant in total cerebellar, right and left cerebellar regions ($p < 0.01$, 0.01 and 0.02). This means that the white matter occupied

Table 1 Baseline data for study subjects

	TDC	ASD
Age (years)		
Mean (range)	7.5 (5–10)	7.9 (5–10)
Gender		
Male	12	14
Female	8	6
CARS score		
Mean (range)		40 (30–56)

Table 2 Comparing total brain, intracranial cavity, white matter, grey matter, and CSF mean volumes in TDC and ASD groups

	Mean ± SD		*p* value
	TDC	ASD	
WM volume cm^3	332.7 ± 30	441.2 ± 59	**< 0.001***
WM volume %	30.7 ± 2.6	32.6 ± 3.1	**0.05***
GM volume cm^3	670.1 ± 85	809.5 ± 60.2	**< 0.001***
GM volume %	61.6 ± 3.4	60 ± 4	0.15
CSF volume cm^3	68.8 ± 9.9	84.5 ± 26.8	**0.01***
CSF volume %	6.4 ± 1.3	6.3 ± 2	0.77
Brain volume (WM ± GM) cm^3	10,003.5 ± 95.2	1250.7 ± 78	**< 0.001***
Brain volume (GM ± WM) %	92.4 ± 1.4	92.5 ± 2	0.77
Intracranial cavity volume cm^3	1085.5 ± 89.1	1351 ± 75.7	**< 0.001***
Intracranial cavity volume %	100	100	

Bold indicates statistically significant

*Statistically significant difference

Table 3 Comparing different brain regions' mean volumes between TDC and ASD groups

	Mean ± SD		*p* value
	TDC	ASD	
Cerebrum total volume cm^3	893.4 ± 79.1	1120.9 ± 74.8	**< 0.001***
Cerebrum total volume %	82.3 ± 1.1	82.9 ± 2.1	0.23
Right cerebrum volume cm^3	447.2 ± 39.2	561.1 ± 37.9	**< 0.001***
Right cerebrum volume %	41.2 ± 0.6	41.5 ± 1.1	0.25
Left cerebrum volume cm^3	446.3 ± 30	559.8 ± 37.1	**< 0.001***
Left cerebrum volume %	41.1 ± 0.6	41.4 ± 1	0.23
Cerebellum total volume cm^3	103.2 ± 15.9	121.2 ± 9.1	**< 0.001***
Cerebellum total volume %	9.5 ± 0.7	9.0 ± 0.7	0.03*
Right cerebellum volume cm^3	51.6 ± 7.6	60.3 ± 5.3	**< 0.001***
Right cerebellum volume %	4.7 ± 0.3	4.5 ± 0.4	0.02*
Left cerebellum volume cm^3	51.6 ± 8.3	60.9 ± 4.1	**< 0.001***
Left cerebellum volume %	4.7 ± 0.4	4.5 ± 0.3	0.05*
Vermis volume cm3	6.9 ± 0.8	8.6 ± 0.7	**< 0.001***
Vermis volume %	0.6 ± 0.03	0.6 ± 0.05	0.54
Brainstem volume cm3	13.2 ± 0.8	16.5 ± 1.5	**< 0.001***
Brainstem volume %	1.2 ± 0.1	1.2 ± 0.1	0.91

Bold indicates statistically significant

*Statistically significant difference

larger percentage of the brain volume at the expense of grey matter (Fig. 1).

All the social brain, repetitive restricted behavior and mirror neuron system components showed statistically significant larger size at both sides, yet all these regions showed no statistically significant difference in mean cortical thickness, except for the entorhineal area which showed statistically significant higher mean cortical thickness at both sides ($p < 0.001$ and $p < 0.003$ at the right and left sides, respectively) (Figs. 2, 3, 4, 5 and 6).

Table 4 Comparing mean volumes of different white matter areas between TDC and ASD groups

	Mean ± SD		*p* value
	TDC	ASD	
WM volume cm^3	332.7 ± 30	441.2 ± 59	**0.001***
WM volume %	30.7 ± 2.6	32.6 ± 3.1	**0.05***
Cerebrum WM total volume cm^3	315 ± 27.9	415.4 ± 53.9	**0.001***
Cerebrum WM total volume %	29.1 ± 2.4	30.7 ± 2.1	0.07
Right cerebrum WM volume cm^3	158.3 ± 13.6	208.6 ± 28.6	**0.001***
Right cerebrum WM volume %	14.6 ± 1.2	15.4 ± 1.6	0.09
Left cerebrum WM volume cm^3	156.7 ± 14.3	206.8 ± 25.3	**0.001***
Left cerebrum WM volume %	14.5 ± 1.2	15.3 ± 1.3	**0.05***
Cerebellum WM total volume cm^3	17.7 ± 2.4	25.8 ± 6.8	**0.001***
Cerebellum WM total volume %	1.6 ± 0.2	1.9 ± 0.4	**0.02***
Right cerebellum WM volume cm^3	8.9 ± 1.2	13.2 ± 3.8	**0.001***
Right cerebellum WM volume %	0.8 ± 0.1	0.9 ± 0.2	**0.03***
Left cerebellum WM volume cm^3	8.7 ± 1.2	12.6 ± 3.1	**0.001***
Left Cerebellum WM volume %	0.81 ± 0.12	0.93 ± 0.19	**0.02***

Bold indicates statistically significant

*Statistically significant difference

Table 5 Comparing mean volumes of different grey matter areas between TDC and ASD groups

	Mean ± SD		*p* value
	TDC	ASD	
GM volume cm^3	670.1 ± 85	809.5 ± 60.2	**< 0.001***
GM volume %	61.6 ± 3.4	60 ± 4	0.15
Subcortical GM volume cm^3	37.9 ± 4	45.4 ± 3	**< 0.001***
Subcortical GM volume %	3.5 ± 0.1	3.4 ± 0.2	0.007
Cortical GM volume cm3	540.5 ± 66.3	660.1 ± 60.7	**< 0.001***
Cortical GM volume %	49.7 ± 2.9	48.9 ± 3.8	0.45
Cerebrum GM total volume cm^3	578.4 ± 70.2	705.5 ± 60.3	**< 0.001***
Cerebrum GM total volume %	53.2 ± 3	52.2 ± 3.9	0.39
Cerebrum GM right volume cm^3	288.8 ± 35.1	352.5 ± 31.3	**< 0.001***
Cerebrum GM right volume %	26.6 ± 1.5	26.1 ± 2	0.41
Cerebrum GM left volume cm^3	289.6 ± 35.1	353 ± 31.1	**< 0.001***
Cerebrum GM left volume %	26.6 ± 1.5	26.1 ± 1.9	0.37
Cerebellum GM total volume cm^3	92.4 ± 16.2	104 ± 12	**0.01***
Cerebellum GM total volume %	8.5 ± 0.8	7.7 ± 1	**0.01***
Cerebellum GM right volume cm^3	42.7 ± 7.5	47.1 ± 6.8	**0.05***
Cerebellum GM right volume %	3.9 ± 0.4	3.5 ± 0.6	**0.01***
Cerebellum GM left volume cm^3	42.9 ± 8	48.3 ± 5.1	**0.02***
Cerebellum GM left volume %	3.9 ± 0.4	3.6 ± 0.4	**0.02***

Bold indicates statistically significant

*Statistically significant difference

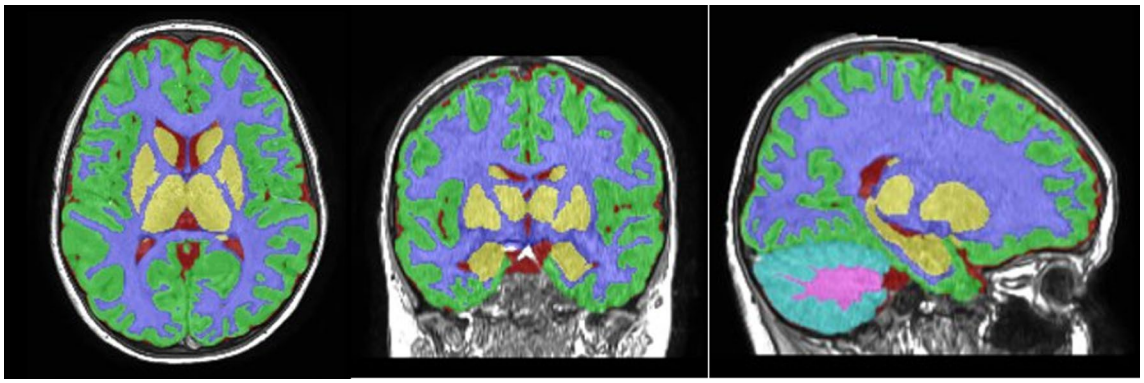

Fig. 1 Selected axial, coronal and sagittal images show color-coded segmentation of different structures of the brain. Cortical grey matter: display in green. Deep grey matter: display in yellow. White matter: display in purple. Cerebrospinal fluid: displayed in red. Cerebellar gray matter: display in blue. Cerebellar white matter: displayed in pink

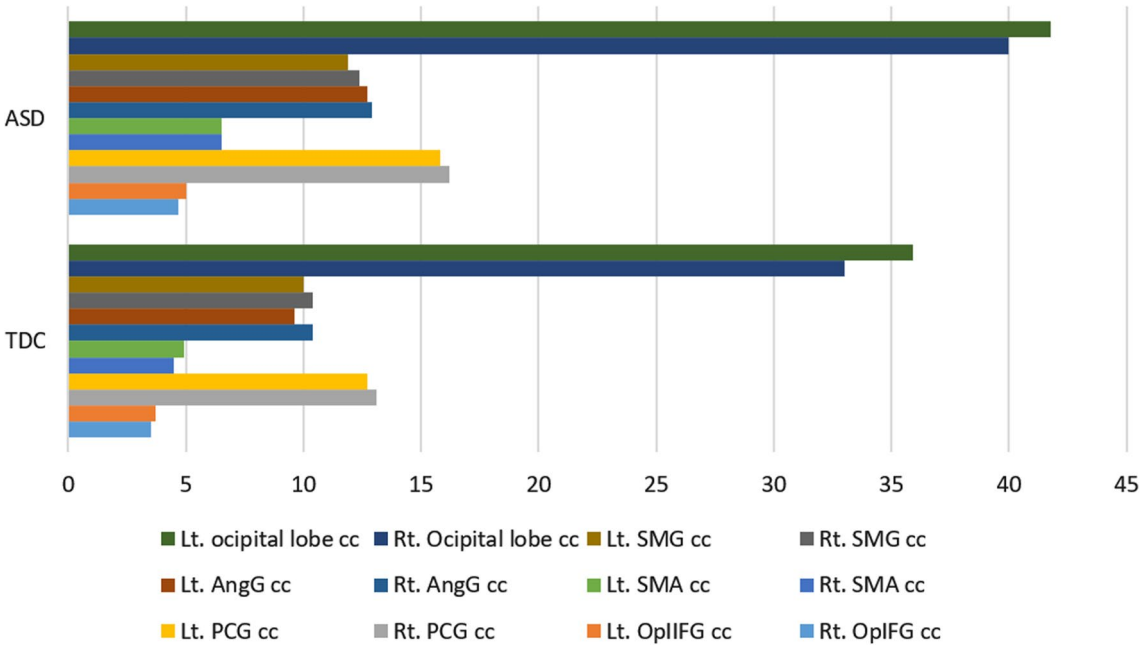

Fig. 2 Mean volume of different mirror neuron system components in TDC and ASD groups. SMG Supramarginal gyrus, AngG Angular gyrus, SMA Supplementry motor area, PCG Precentral gyrus, OpIFG Opercular inferior frontal gyrus

For white matter microstructure and structural connectivity changes using DTI measurements, global statistically significant ($p<0.001$) higher mean FA values among ASD group in comparison with TDC group were seen (Fig. 7), including commisural fibers (Splenium of corpus callosum) (Fig. 8), association fibers (hippocampus, sagittal stratum, superior longitudinal fasciculus) (Fig. 9), projection fibers (anterior limb of internal capsule, retro-lenticular part of internal capsule, superior corona radiata, cerebral peduncles, cortico-spinal tracts and posterior thalamic radiation) (Fig. 10) and brain stem tracts (superior cerebellar peduncles, middle cerebellar peduncles and pontine crossing tracts) (Fig. 11).

Discussion

Autism spectrum disorder shows increasing prevalence which doubled in the last decade, with no consensus found regarding the neuropathologic aspects of the disease and absence of definite neuroimaging findings supporting the diagnosis.

This case–control study was conducted on 20 patients diagnosed with autism spectrum disorder according to DSM-5 criteria and CARS, with age range 5 to 10 years

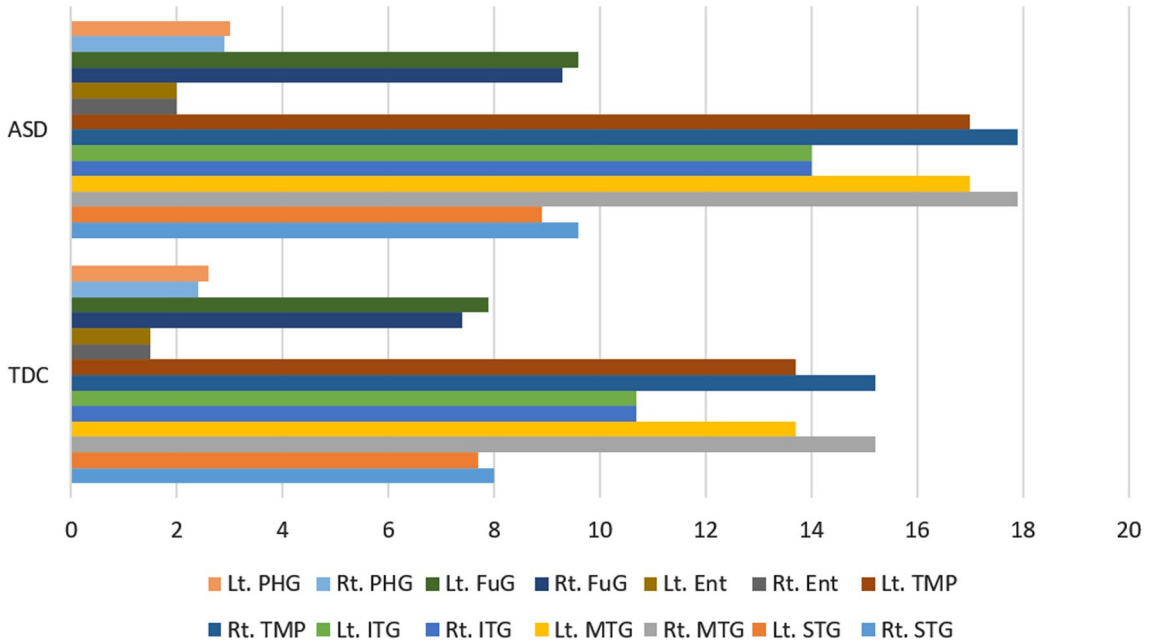

Fig. 3 Anterior temporal lobe (component of social brain) mean volume in TDC and ASD groups. PHG Parahippocampal gyrus, FuG Fusiform gyrus, Ent Entorhineal cortex, TMP Temporal pole, ITG Inferior temporal gyrus, MTG Middle temporal gyrus, STG Superior temporal gyrus

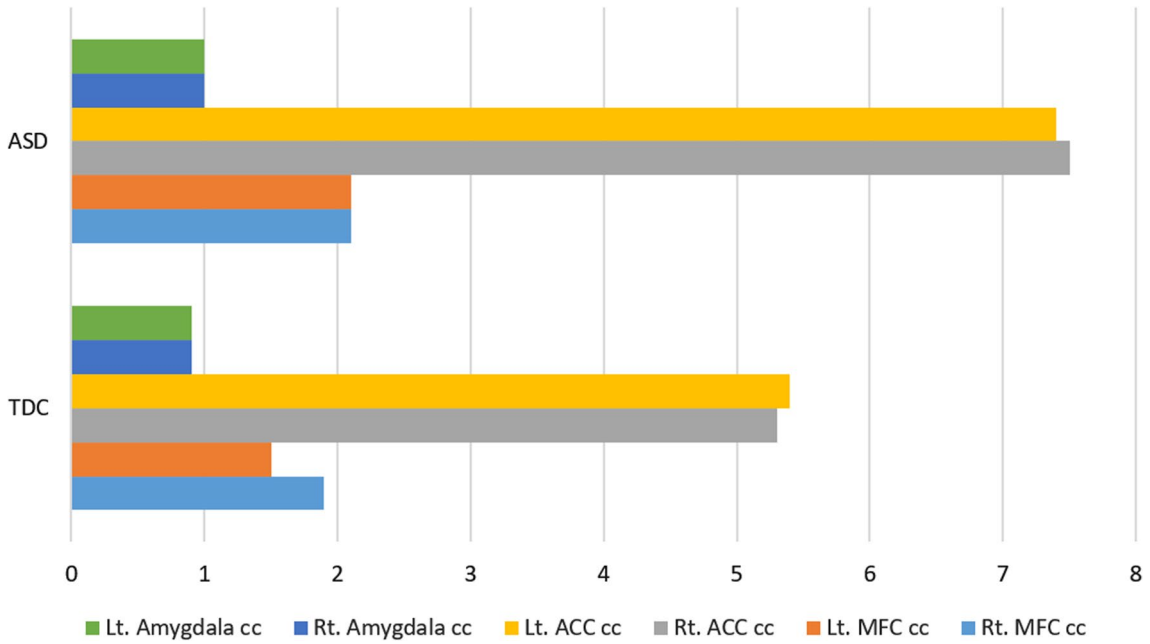

Fig. 4 Social brain components' (other than anterior temporal lobe) mean volume in TDC and ASD groups. ACC Anterior cingulate cortex, MFC Medial frontal cortex

(mean age 7.9 years). 14 males and 6 females, with the male to female ratio equals 2.3:1, which appears consistent with reports of this ratio ranging between 2:1 and 4.2:1 [25]. Children diagnosed with ASD showed mean CARS score of 40 (range 30–56).

Twenty age- and sex-matched typically developing children were included as control group, with age range 5–10 years (mean age 7.5 years). This group included 12 males and 8 females.

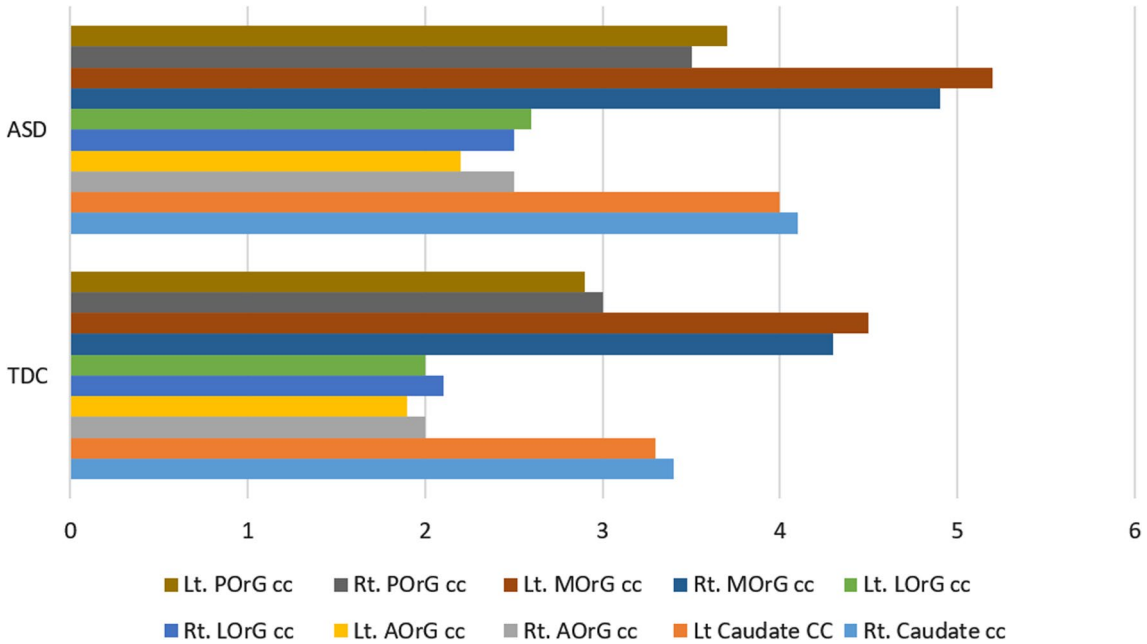

Fig. 5 Repetitive behavior brain components' mean volume in TDC and ASD groups. POrG Posterior orbital gyrus, MOrG Medial orbital gyrus, LOrG Lateral orbital gyrus, AOrG Anterior orbital gyrus

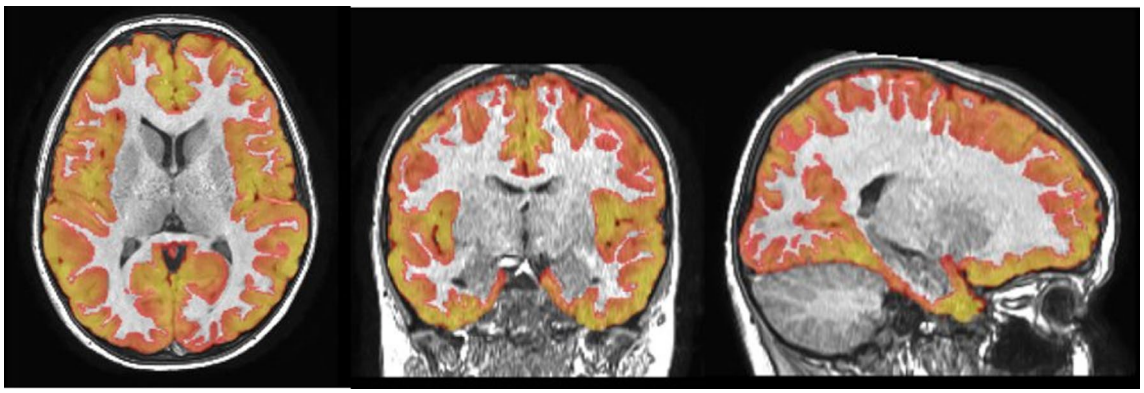

Fig. 6 Selected axial, coronal and sagittal images showing color-coded segmentation of cortical grey matter during cortical thickness measurement

In this study, two parameters were used to assess macrostructure, microstructure, and structural connectivity in autistic brain in comparison to typically developing brain.

Brain macrostructure assessment using volumetric measures of different brain structures and regions showed statistically significant larger intracranial cavity volume ($p < 0.001$), brain volume ($p < 0.001$), white matter ($p < 0.001$), grey matter ($p < 0.001$) and CSF ($p = 0.01$) volumes in ASD brains in comparison with TDC. This larger size appeared global involving all brain regions, including the mirror neuron system, social brain and repetitive behavior brain components ($p < 0.001$), with white matter seen occupying statistically significant larger percentage at the left cerbral hemisphere, as well as right and left cerebellar hemispheres ($p = 0.05$, 0.03 and 0.02) but not the right cerebral hemisphere ($p = 0.09$). The previous findings support one of the most prominent theories in ASD neuropathology that states the autistic brain undergoes period of precocious growth followed by deceleration in age related growth [1]. This finding was also supported by multiple other studies, where Nagae et. al. found that at early ages, an abnormal growth spurt resulting in marked greater brain volumes occurs in ASD patients

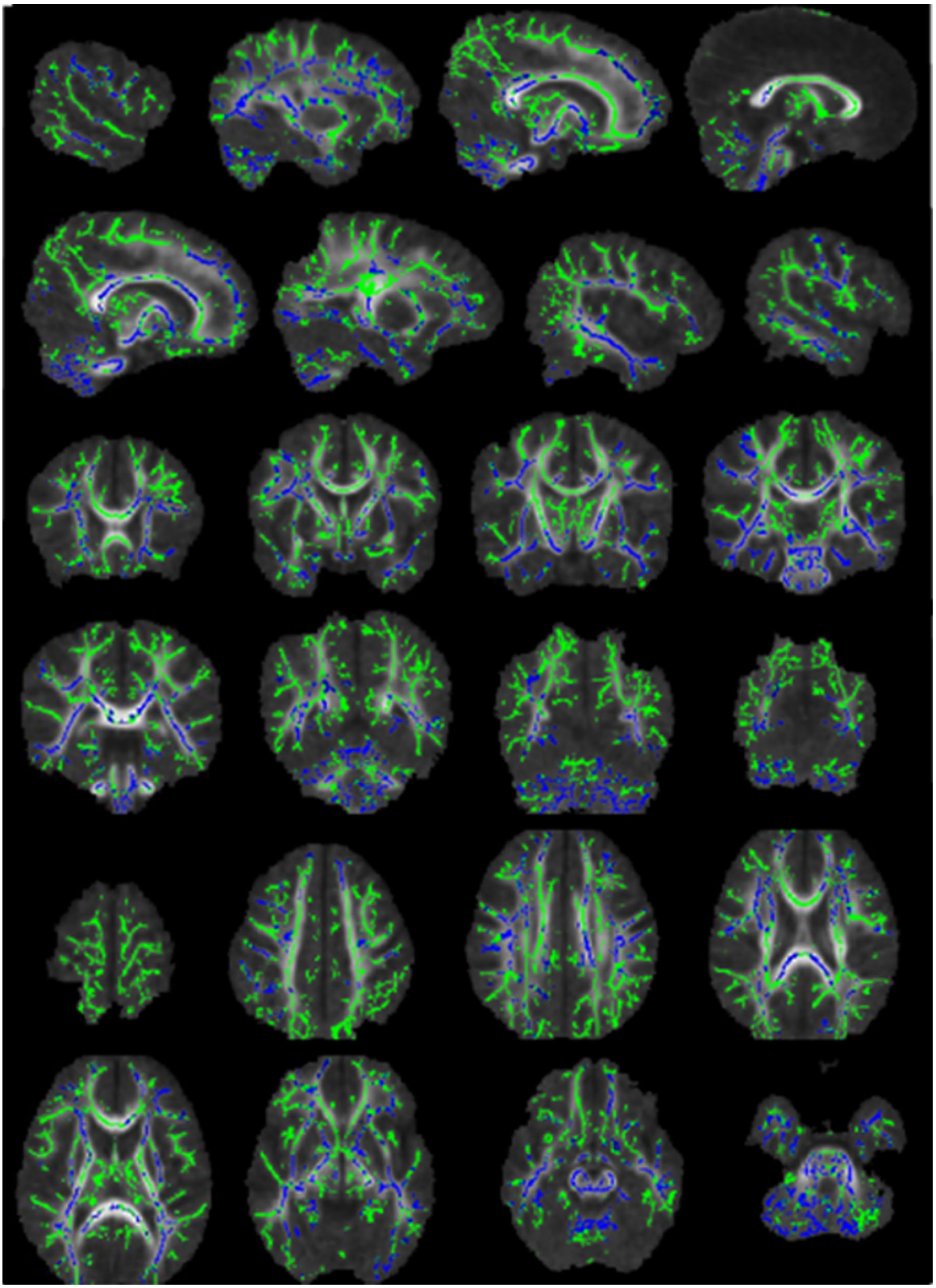

Fig. 7 Sagittal (Rt. To Lt.), coronal (anterior to posterior) and axial (cranial to caudal) Images of the brain showing global statistically significant higher mean FA values among ASD group in comparison to TDC group (blue color), while no statistically significant higher mean FA values were detected in the TDC group (supposed to appear in red color)

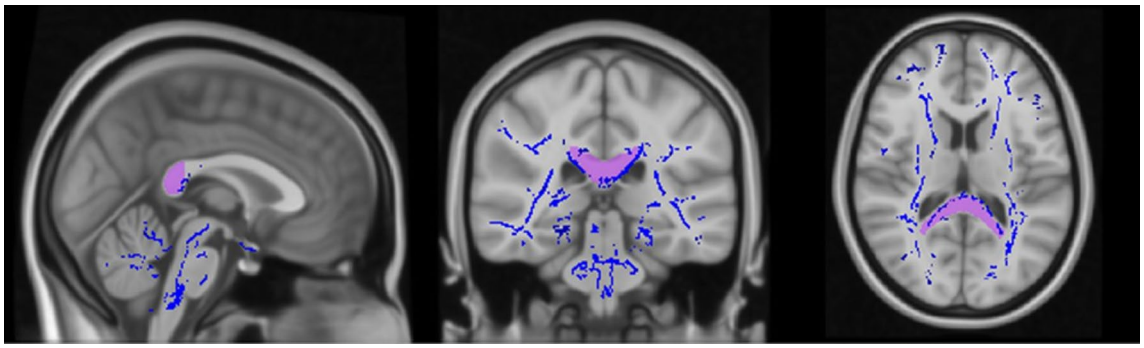

Fig. 8 Splenim (displayed in purple) of corpus callosum showing statistically significant (p value < 0.001) higher mean FA value in ASD group compared to TDC group displayed in blue

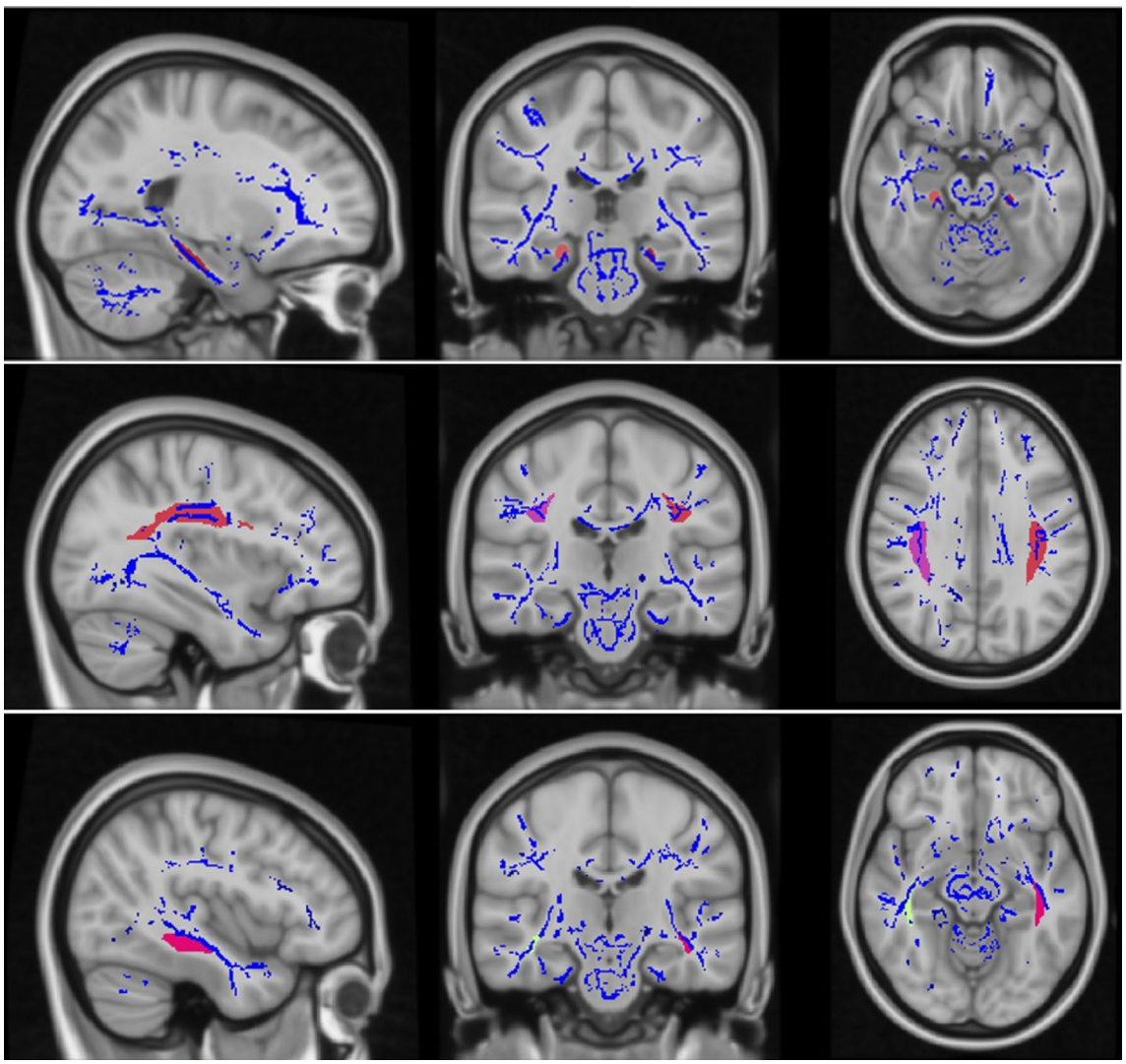

Fig. 9 Association fibers; hippocampus, sagittal stratum, superior longitudinal fasciculus displayed from top to bottom rows, respectively, showing statistically significant (p value < 0.001) higher mean FA value in ASD group compared to TDC group displayed in blue

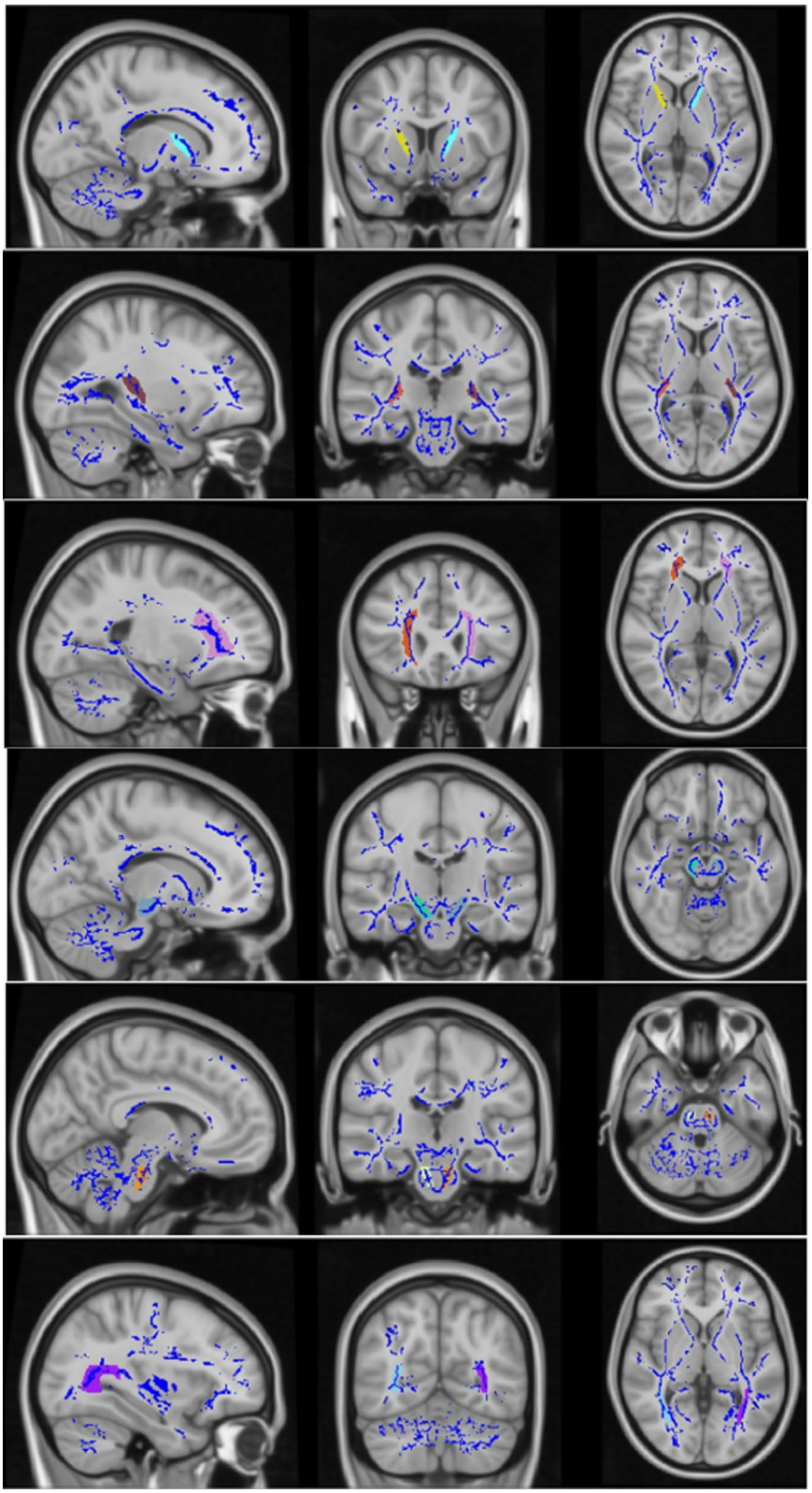

Fig. 10 Projection fibers; anterior limb of internal capsule, retro-lenticular part of internal capsule, superior corona radiata, cerebral peduncles, cortico-spinal tracts and posterior thalamic radiation from top to bottom row, respectively, showing statistically significant (p value < 0.001) higher mean FA value in ASD group compared to TDC group displayed in blue

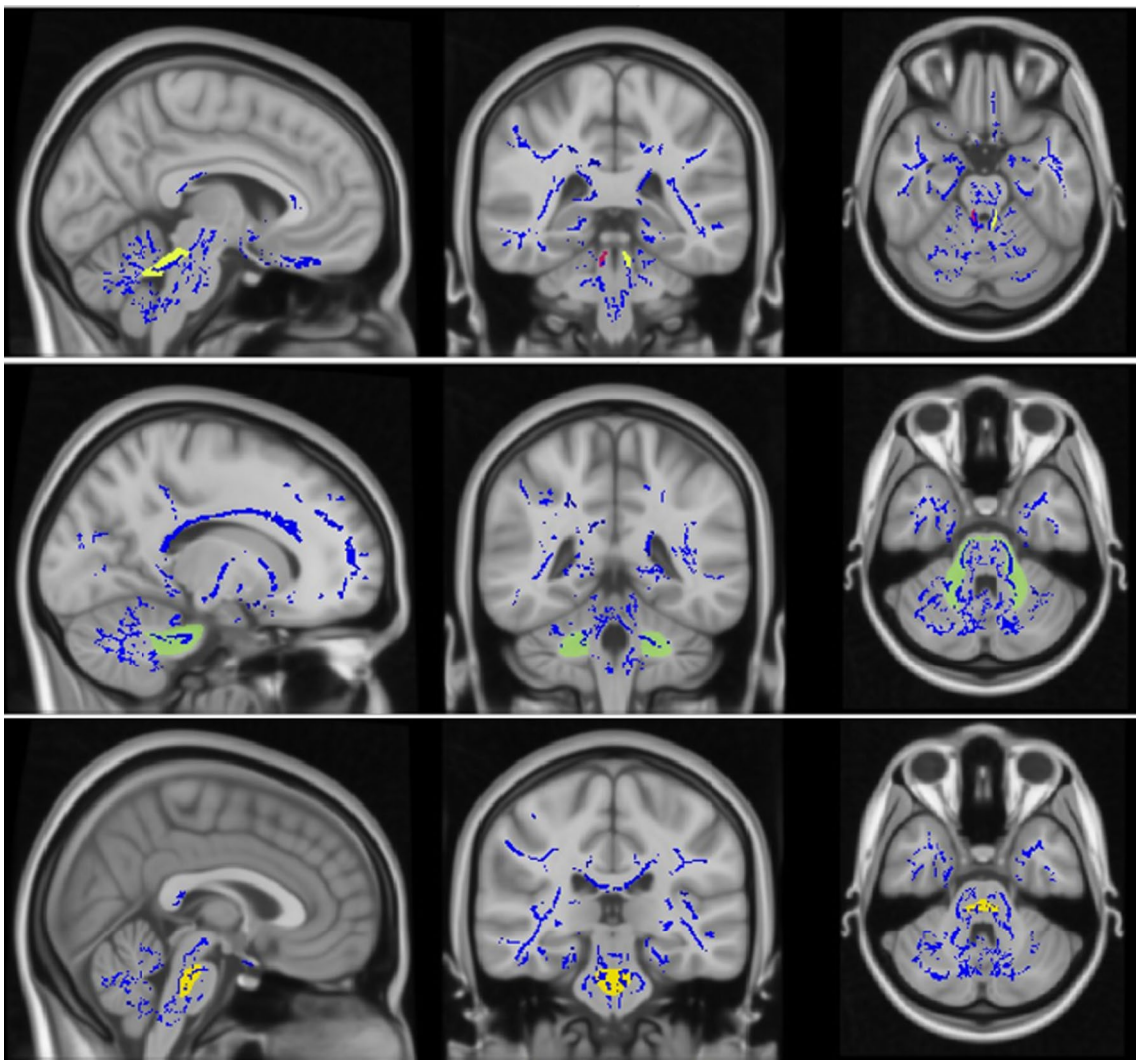

Fig. 11 Brain stem tracts; superior cerebellar peduncles, middle cerebellar peduncles and pontine crossing tracts from top to bottom row, respectively, showing statistically significant (p value < 0.001) higher mean FA value in ASD group compared to TDC group displayed in blue

with abnormality mainly in white matter volume suggesting abnormal white matter maturation [34]. Herbert et al. [22] also stated that this abnormal brain enlargement is disproportionately accounted for by larger white matter volume rather than grey matter volume.

For cortical thickness (CT) measurements, no detectable increase in cortical thickness was noted at different brain regions, except at the entorhinal cortex bilaterally, this means that the increase in grey matter volume may reflect increase in cortical surface area secondary to cortical white matter overgrowth rather than increase in cortical thickness. This finding is supported by Uddin et. al. who described increase in grey matter volume that is likely due to accelerated expansion in cortical surface area of grey matter rather than increase in cortical thickness, they postulated that this expansion is associated with impaired maturation of the cortical white matter [48]. But Squarcina et al. found that CT increased in various brain regions in ASD subjects, confirming their role in the pathogenesis of this condition. Considering the brain development curve during ages, these changes in CT may normalize during development [46].

Other studies reported both increase and decrease in CT in different brain regions [12, 24, 32, 38, 40, 41] in ASD subjects. Cortical development trajectories in ASD subjects report an early hyperplasia in the first years of life [9, 10], followed by nearly normalization in successive stages [24]; this confirms the hypothesis of early brain overgrowth, followed by volume plateau and decline, could be considered a biologic hallmark of this disease.

The entorhinal area is part of the anterior temporal lobe, representing part of social brain as well as important part in memory formation. It displays statistically significant larger mean volume ($p < 0.001$ at both sides) as well as larger cortical thickness ($p < 0.001$ at right side, $p = 0.003$ uat left side).Up to our knowledge, no studies examined the relation between entorhinal cortex CT and ASD.

Brain microstructure and structural connectivity assessment using Diffusion Tensor Imaging showed statistically significant global increase in mean fractional anisotropy ($p < 0.001$) is noted in ASD group compared to TDC group. This increase in mean FA when viewed in the context of the previously discussed evidence of early anatomical brain overgrowth of grey and white matter in ASD could be interpreted as evidence of possible precocious maturation of white matter in children with ASD.

This finding is also supported by Bashat et al. and Weinestin et al., where both studies showed increased FA value in multiple white matter trajectories including corpus callosum, internal capsule, superior longitudinal fasciculus and cingulum [7, 50], and also Ouyang et al. found unidirectional global increase in white matter mean FA, most evident in children younger than 4 years of age, with mixed results seen in the age group of 2–7 years, compared to progressive development and increase in mean FA in TDC group. These findings suggest that the early higher white matter microstructural integrity reflect abnormal neural patterning, connectivity and pruning which may contribute to aberrant behavioral and cognitive development in ASD [37]. Clery et al. [13], Vissers et al. [49] and Keehn et al. [27] also showed increased functional connectivity in different tracts in ASD brain when compared to TDC brain, and this can also be another reflection of underlying increase in structural connectivity.

At the same time, some of prior Diffusion Tensor Imaging (DTI) studies, systematic reviews [47] and meta-analyses [16] have consistently reported reduced FA in the white matter of school-aged children [15, 23, 31] and adults with ASD [8, 11, 19, 28, 29, 36], while Fingher et. al. found variable inconsistent findings regarding FA values in ASD [17].

Limitations

Sample size is one of the limitations of this study with larger samples needed in further studies to create diagnostic cutoff values. Also, the temporal changes in brain structure with age necessitate the need for further follow-up studies to assess these changes. Obtaining the DTI and 3D-T1 sequences remains relatively lengthy for the autistic children, necessitating the need for sedation to achieve motion free images.

Conclusions

This study showed significant differences between autistic and typically developing brain at the level of both micro- and macrostructure. This difference, which appears most significant in white matter, supports the underlying hypothesis of ASD pathogenesis and can be used as preliminary step in creating a database for setting cutoff values for diagnosis of ASD by imaging in addition to clinical assessment.

Abbreviations

ASD	Autism spectrum disorder
CT	Cortical thickness
DTI	Diffusion tensor imaging
FA	Fractional anisotropy
MRI	Magnetic resonance imaging
TBSS	Tract-based spatial statistics
TDC	Typically developing children

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Author contributions

AG suggested the research idea, minimized the obstacles to the team of work and had the major role in imaging interpretation. TK supervised the study with significant contribution to design the methodology, manuscript revision and preparation. Study subjects were examined, diagnosed and referred by OE. LS was responsible for imaging interpretation, research data collection, processing, and analysis. All authors read and approved the final manuscript for submission.

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Availability of data and materials

The datasets used and analyzed in this study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate

The protocol was reviewed and approved by the Ethics Committee of faculty of medicine, Suez Canal University. Number of ethical approval 4009.

Consent for publication

A written consent for publication was obtained from the legal guardians of the children and approved by the Ethics Committee of Faculty of Medicine, Suez Canal University.

Competing interests

The authors declare that they have no competing interests.

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References

1. Amaral DG, Schumann CM, Nordahl CW (2008) Neuroanatomy of autism. Trends Neurosci 31(3):137–145
2. Andersson JL, Jenkinson M, Smith S (2007) Non-linear optimisation FMRIB technical report TR07JA1. University of Oxford FMRIB Centre, Oxford
3. Andersson JL, Jenkinson M, Smith S (2007) Non-linear registration, aka spatial normalisation FMRIB technical report TR07JA2. FMRIB Anal Group Univ Oxford 2(1):e21

4. American Psychiatric Association (2013) Diagnostic and statistical manual of mental disorders (DSM-V). American Psychiatric Association, Arlington
5. Baio J, Wiggins L, Christensen DL, Maenner MJ, Daniels J, Warren Z, Dowling NF (2018) Prevalence of autism spectrum disorder among children aged 8 years—autism and developmental disabilities monitoring network, 11 sites, United States, 2014. MMWR Surveill Summ 67(6):1
6. Baribeau DA, Dupuis A, Paton TA, Hammill C, Scherer SW, Schachar RJ, Arnold PD, Szatmari P, Nicolson R, Georgiades S, Crosbie J (2019) Structural neuroimaging correlates of social deficits are similar in autism spectrum disorder and attention-deficit/hyperactivity disorder: analysis from the POND Network. Transl Psychiatry 9:72
7. Bashat DB, Kronfeld-Duenias V, Zachor DA, Ekstein PM, Hendler T, Tarrasch R, Sira LB (2007) Accelerated maturation of white matter in young children with autism: a high b value DWI study. Neuroimage 37(1):40–47
8. Bletsch A, Schäfer T, Mann C, Andrews DS, Daly E, Gudbrandsen M, Ecker C (2021) Atypical measures of diffusion at the gray-white matter boundary in autism spectrum disorder in adulthood. Hum Brain Mapp 42(2):467–484
9. Brun CC, Nicolson R, Leporé N, Chou YY, Vidal CN, DeVito TJ, Thompson PM (2009) Mapping brain abnormalities in boys with autism. Hum Brain Mapp 30(12):3887–3900
10. Carper RA, Moses P, Tigue ZD, Courchesne E (2002) Cerebral lobes in autism: early hyperplasia and abnormal age effects. Neuroimage 16(4):1038–1051
11. Chiang HL, Chen YJ, Lin HY, Tseng WYI, Gau SSF (2017) Disorder-specific alteration in white matter structural property in adults with autism spectrum disorder relative to adults with ADHD and adult controls. Hum Brain Mapp 38(1):384–395
12. Chung MK, Robbins SM, Dalton KM, Davidson RJ, Alexander AL, Evans AC (2005) Cortical thickness analysis in autism with heat kernel smoothing. Neuroimage 25(4):1256–1265
13. Clery H, Andersson F, Bonnet-Brilhault F, Philippe A, Wicker B, Gomot M (2013) fMRI investigation of visual change detection in adults with autism. NeuroImage Clin 2:303–312
14. Contarino VE, Bulgheroni S, Annunziata S, Erbetta A, Riva D (2016) Widespread focal cortical alterations in autism spectrum disorder with intellectual disability detected by threshold-free cluster enhancement. Am J Neuroradiol 37(9):1721–1726
15. Dimond D, Schuetze M, Smith RE, Dhollander T, Cho I, Vinette S, Bray S (2019) Reduced white matter fiber density in autism spectrum disorder. Cereb Cortex 29(4):1778–1788
16. Di X, Azeez A, Li X, Haque E, Biswal BB (2018) Disrupted focal white matter integrity in autism spectrum disorder: a voxel-based meta-analysis of diffusion tensor imaging studies. Prog Neuropsychopharmacol Biol Psychiatry 82:242–248
17. Fingher N, Dinstein I, Ben-Shachar M, Haar S, Dale AM, Eyler L, Courchesne E (2017) Toddlers later diagnosed with autism exhibit multiple structural abnormalities in temporal corpus callosum fibers. Cortex 97:291–305
18. Franz L, Chambers N, von Isenburg M, de Vries PJ (2017) Autism spectrum disorder in Sub-saharan Africa: a comprehensive scoping review. Autism Res 10(5):723–749
19. Haigh SM, Keller TA, Minshew NJ, Eack SM (2020) Reduced white matter integrity and deficits in neuropsychological functioning in adults with autism spectrum disorder. Autism Res 13(5):702–714
20. Hansen SN, Schendel DE, Parner ET (2015) Explaining the increase in the prevalence of autism spectrum disorders: the proportion attributable to changes in reporting practices. JAMA Pediatr 169(1):56–62
21. Hegarty JP, Gengoux GW, Berquist KL, Millán ME, Tamura SM, Karve S, Hardan AY (2019) A pilot investigation of neuroimaging predictors for the benefits from pivotal response treatment for children with autism. J Psychiatr Res 111:140–144
22. Herbert MR, Ziegler DA, Deutsch CK, O'brien LM, Lange N, Bakardjiev A, Caviness VJ (2003) Dissociations of cerebral cortex, subcortical and cerebral white matter volumes in autistic boys. Brain 126(5):1182–1192
23. Hong SJ, Hyung B, Paquola C, Bernhardt BC (2019) The superficial white matter in autism and its role in connectivity anomalies and symptom severity. Cereb Cortex 29(10):4415–4425
24. Hyde KL, Samson F, Evans AC, Mottron L (2010) Neuroanatomical differences in brain areas implicated in perceptual and other core features of autism revealed by cortical thickness analysis and voxel-based morphometry. Hum Brain Mapp 31(4):556–566
25. Jaarsma P, Welin S (2012) Autism as a natural human variation: reflections on the claims of the neurodiversity movement. Health Care Anal 20(1):20–30
26. José VM, Pierrick C (2016) volBrain: an online MRI brain volumetry system. Front Neuroinform 10:30
27. Keehn B, Shih P, Brenner LA, Townsend J, Müller RA (2013) Functional connectivity for an "island of sparing" in autism spectrum disorder: an fMRI study of visual search. Hum Brain Mapp 34(10):2524–2537
28. Koolschijn PCM, Caan MW, Teeuw J, Olabarriaga SD, Geurts HM (2017) Age-related differences in autism: the case of white matter microstructure. Hum Brain Mapp 38(1):82–96
29. Lei J, Lecarie E, Jurayj J, Boland S, Sukhodolsky DG, Ventola P, Jou RJ (2019) Altered neural connectivity in females, but not males with autism: Preliminary evidence for the female protective effect from a quality-controlled diffusion tensor imaging study. Autism Res 12(10):1472–1483
30. Li SJ, Wang Y, Qian L, Liu G, Liu SF, Zou LP, Ma L (2018) Alterations of white matter connectivity in preschool children with autism spectrum disorder. Radiology 288(1):209–217
31. Libero LE, Burge WK, Deshpande HD, Pestilli F, Kana RK (2016) White matter diffusion of major fiber tracts implicated in autism spectrum disorder. Brain Connect 6(9):691–699
32. Misaki M, Wallace GL, Dankner N, Martin A, Bandettini PA (2012) Characteristic cortical thickness patterns in adolescents with autism spectrum disorders: interactions with age and intellectual ability revealed by canonical correlation analysis. Neuroimage 60(3):1890–1901
33. Müller RA, Fishman I (2018) Brain connectivity and neuroimaging of social networks in autism. Trends Cogn Sci 22(12):1103–1116
34. Nagae LM, Zarnow DM, Blaskey L, Dell J, Khan SY, Qasmieh S, Roberts TPL (2012) Elevated mean diffusivity in the left hemisphere superior longitudinal fasciculus in autism spectrum disorders increases with more profound language impairment. Am J Neuroradiol 33(9):1720–1725
35. National Research Council (2001) Educating children with Autism. National Academy Press, Washington DC
36. Nickel K, Tebartz van Elst L, Perlov E, Endres D, Müller GT, Riedel A, Maier S (2017) Altered white matter integrity in adults with autism spectrum disorder and an IQ> 100: a diffusion tensor imaging study. Acta Psychiatr Scand 135(6):573–583
37. Ouyang M, Cheng H, Mishra V, Gong G, Mosconi MW, Sweeney J, Huang H (2016) Atypical age-dependent effects of autism on white matter microstructure in children of 2–7 years. Hum Brain Mapp 37(2):819–832
38. Pagnozzi AM, Conti E, Calderoni S, Fripp J, Rose SE (2018) A systematic review of structural MRI biomarkers in autism spectrum disorder: a machine learning perspective. Int J Dev Neurosci 71:68–82
39. Rorden C, Brett M (2000) Stereotaxic display of brain lesions. Behav Neurol 12(4):191–200
40. Sarovic D, Hadjikhani N, Schneiderman J, Lundström S, Gillberg C (2020) Autism classified by magnetic resonance imaging: a pilot study of a potential diagnostic tool. Int J Methods Psychiatr Res 29(4):1–18
41. Scheel C, Rotarska-Jagiela A, Schilbach L, Lehnhardt FG, Krug B, Vogeley K, Tepest R (2011) Imaging derived cortical thickness reduction in high-functioning autism: key regions and temporal slope. Neuroimage 58(2):391–400
42. Schopler E, Reichler RJ, Renner BR (2010) The childhood autism rating scale (CARS). WPS, Los Angeles
43. Smith SM (2002) Fast robust automated brain extraction. Hum Brain Mapp 17(3):143–155
44. Smith SM, Jenkinson M, Woolrich MW, Beckmann CF, Behrens TE, Johansen-Berg H, Matthews PM (2004) Advances in functional and structural MR image analysis and implementation as FSL. Neuroimage 23:S208–S219
45. Smith SM, Jenkinson M, Johansen-Berg H, Rueckert D, Nichols TE, Mackay CE, Behrens TE (2006) Tract-based spatial statistics: voxelwise analysis of multi-subject diffusion data. Neuroimage 31(4):1487–1505
46. Squarcina L, Nosari G, Marin R, Castellani U, Bellani M, Bonivento C, Brambilla P (2021) Automatic classification of autism spectrum disorder in children using cortical thickness and support vector machine. Brain Behav 11(8):e2238
47. Travers BG, Adluru N, Ennis C, Tromp DP, Destiche D, Doran S, Alexander AL (2012) Diffusion tensor imaging in autism spectrum disorder: a review. Autism Res 5(5):289–313

48. Uddin LQ, Supekar K, Menon V (2013) Reconceptualizing functional brain connectivity in autism from a developmental perspective. Front Hum Neurosci 7:458
49. Vissers ME, Cohen MX, Geurts HM (2012) Brain connectivity and high functioning autism: a promising path of research that needs refined models, methodological convergence, and stronger behavioral links. Neurosci Biobehav Rev 36(1):604–625
50. Weinstein M, Ben-Sira L, Levy Y, Zachor DA, Itzhak EB, Artzi M, Bashat DB (2011) Abnormal white matter integrity in young children with autism. Hum Brain Mapp 32(4):534–543

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