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The utility of volumetric MRI in assessment of volume changes in ventral diencephalon in autistic children

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Abstract

Background Autism spectrum disorder (ASD) is a neurobehavioural disorder, characterized by abnormal affiliative and socio-emotional responses which are generally regulated by certain neuropeptides in the hypothalamus (an anatomic component of the ventral diencephalon (VD)). The use of volumetric MRI for studying VD volume change could provide a novel approach for identification of structural brain changes in ASD; this could assist in understanding the pathophysiology of ASD and would reflect on treatment strategies. The aim of the current work was to investigate the role of MRI volumetric analysis of the ventral diencephalon in young children diagnosed with autism spectrum disorder.

Methods Fifty children diagnosed with ASD underwent volumetric brain analysis, on a fully automated MRI brain volumetry system (volBrain), with voxel-based morphometry of various segmental structures of the brain including the VD, using vol2Brain 1.0 pipeline software analysis suite.

Results There were 48 out of 50 children who demonstrated abnormal VD volume which was found below the normal limits compared with reference standard normalized volume. All cases were normocephalic demonstrating normal intra-cranial cavity volumes. Forty out of fifty cases showed increased total volume of grey matter, and eighteen out of fifty cases showed increased total volume of white matter. Regarding the amygdala and hippocampus, there were only two cases (4.0%) which showed slightly increased relative volume of the total amygdala, and two other cases (4.0%) demonstrated increased relative volume of the total hippocampus. Comparison between the autistic patients and normal references revealed a significant difference regarding the VD volume and total volume of grey matter, whereas no significant differences were found regarding the white matter amygdala and hippocampus.

Conclusions Based on the consistent significant volume decrease in the ventral diencephalon in patients with childhood autism, this study concluded that volumetric MRI analysis could be useful for diagnosis of childhood spectrum disorder and could be utilized as a reliable screening method in the clinically vague cases. Further study with a larger sample size including more age groups is recommended for more validation of the results.

Keywords Diencephalon, Magnetic resonance imaging, Neuroimaging, Autism spectrum disorder

Background

Autism spectrum disorder (ASD) is a developmental neurobehavioural disorder characterized by impaired social interaction and communication. The global prevalence of ASD is increasing with estimated value equal to 62/10,000 people, and this could further increase among

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children suffering from other developmental disorders [1, 2].

The ventral diencephalon (VD) is defined as a group of cerebral structures located ventral to the thalamus. They could not be distinguished from each other on standard magnetic resonance imaging (MRI). The relevant and important VD component that would contribute to pathophysiology of ASD is the hypothalamus, and it could support and regulate the affiliative and socio-emotional responses owing to its neuropeptides. Because of its small size and the difficulty regarding its delineation and its volumetric analysis, the studies which are concerning with hypothalamic abnormalities in ASD on MRI are quite few in contrast to other structures like the amygdala and hippocampus [3, 4].

The use of volumetric MRI for studying various brain diseases has been widely applied; it has the advantage of being non-invasive technique which provides high spatial resolution images. The detection of ventral diencephalon volume change using volumetric MRI could provide a novel approach for identification of structural brain changes which occur in autism; this in turn could assist in understanding the pathophysiology of ASD and would directly reflect on the treatment strategy alteration such as early behavioural interference and individualized therapy [5, 6].

The aim of the current work was to investigate the role of MRI volumetric analysis of the ventral diencephalon in young children diagnosed with autism spectrum disorder.

Methods

This observational analytic prospective study was conducted in the MRI unit of our institution from September 2021 to August 2022 after being approved by the Faculty of Medicine Research Ethics Committee. Approval number was 16:3/2021.

Study participants

Fifty five children aged 3–9 years and formally diagnosed with autism spectrum disorder were referred from the neuropsychiatric clinic in paediatric department to the MRI unit for brain MRI study; five cases of them were excluded from the study due to concurrent structural brain anomalies found in MRI. The remaining fifty children were 40 (80%) males and 10 (20%) females with mean age 5.58 ± 1.29 (range was 3–8.5). All fifty patients underwent thorough history taking about their cognitive development and behaviour, assessment of language abilities, as well as complete medical, neurological and hearing examinations. An informed written consent was obtained from child's parents prior to participating in the study.

Inclusion criteria

Inclusion criteria for patients were based on formal clinical diagnosis of ASD in a young child aged 3–9 years, using in-depth developmental evaluation that was done by a trained paediatric neurologist with eight-year experience in paediatric neurology.

Exclusion criteria

Contraindications to MRI study (as in patients with cochlear implant), concurrent congenital heart disease not candidate for sedation, older children above 9 years and patients with structural brain anomalies were the exclusion criteria.

MRI technique

Conventional MRI study of the brain was performed on an Ingenia 1.5 Tesla Philips closed MR scanner using head coil. All children were sedated with chloral hydrate and immobilized on the table during the study. The following sequences were performed for all cases: Sagittal T1W-3D turbo gradient echo (TR/TE 7.5/3.4 ms, matrix 256×216, flip angle 8, duration 7:02 min), coronal T2WI (TR/TE 3163/100 ms, matrix 180×187, slice thickness/gap 5/1 mm, duration 2:10 min), axial FLAIR (TR/TE 8000/92 ms, matrix 240×143, slice thickness/gap 5/1 mm, duration 3:21 min), axial DWI (TR/TE 6000/110 ms, matrix 192×190, slice thickness/gap 5/1 mm, duration 1:13 min) and sagittal T1WI (TR/TE 550/15 ms, matrix 168×131, slice thickness/gap 5/1 mm, duration 1:35 min).

Image analysis

Five radiologists have assessed the conventional brain MRI images independently, and blindly in all cases, their experiences in neuroradiology were 25, 15, 10, 9 and 5 years. Any structural abnormalities or signs of related disease/syndrome were reported for exclusion purpose. Volumetric analysis of the T1W-3D gradient echo images was carried out on a fully automated MRI brain volumetry system (volBrain) which employed a voxel-based morphometry and segmentation of brain macro-structures as well as subcortical regions including the limbic system and VD, and the used software version was vol2Brain 1.0 pipeline software analysis suite (Fig. 1).

Quality control and case validation were done by visual assessment of input image quality before uploading to volBrain software, and also after the volumetric report became ready, a second visual assessment of the processed images was performed on volBrain reports which provide screenshots of one sagittal, one coronal and one axial image. All volumes were presented in absolute values (measured in cm^3) as well as in relative values which

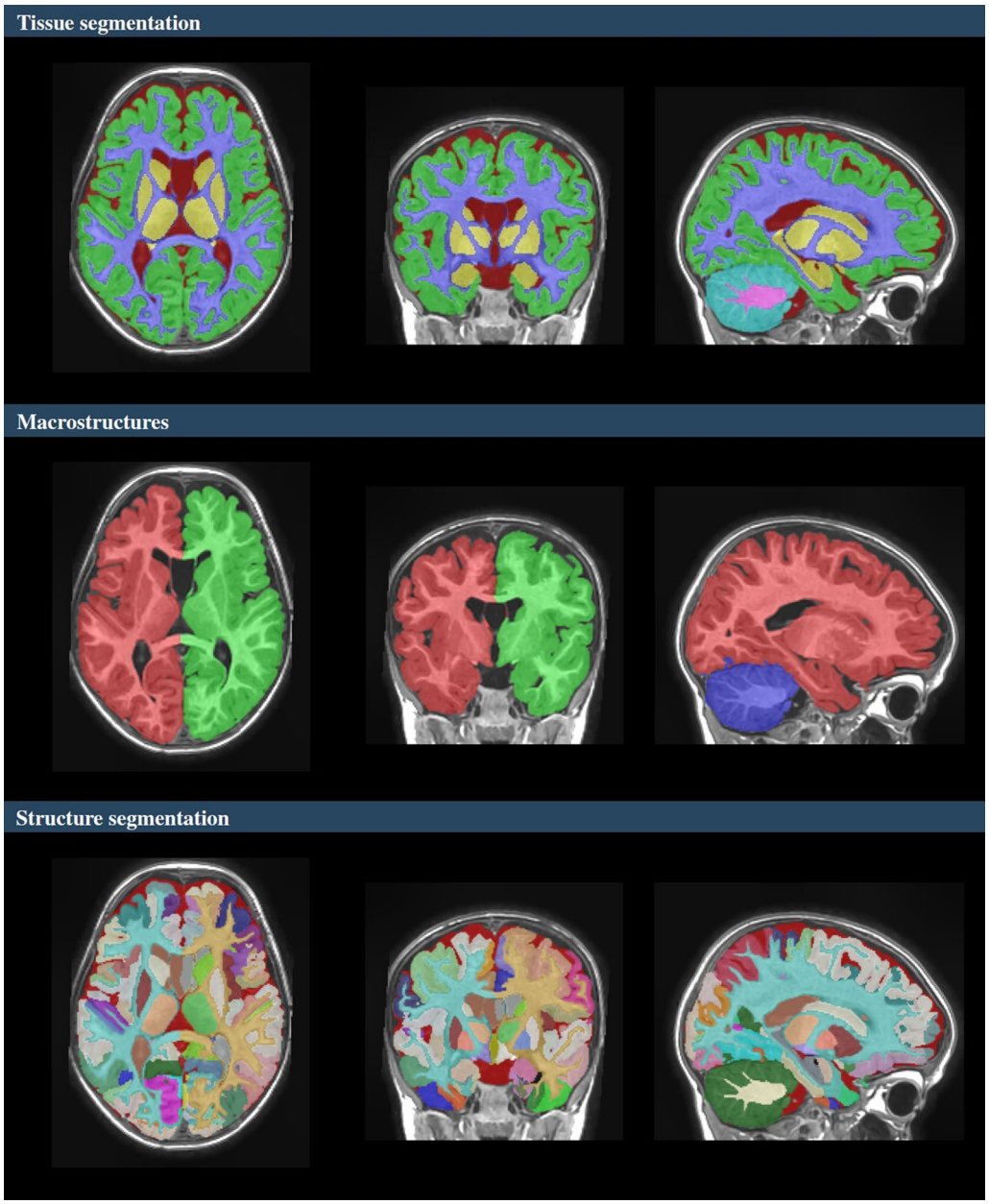


Fig. 1 Tissue and structure segmentations as expressed on vol2Brain volumetry report, the segmental tissues are: cortical, subcortical and cerebellar grey matter, white matter and cerebrospinal fluid (CSF), the macro-structures include the cerebrum, the cerebellum, the vermis and the brainstem

were measured in relation to the intra-cranial cavity volume (ICV). For reference purpose, the obtained values were compared with expected normal limits provided by volBrain software that were 95% of normalized volume in function of sex and age. The library of constructed templates of the vol2Brain software has utilized different public brain datasets covering nearly the entire human life-span and both sexes (all values outside the limits were highlighted in red). The Asymmetry Index is calculated as the difference between right and left volumes divided by their mean (in per cent) [7].

Statistical analysis

Data analysis was performed using SPSS software, version 26. The qualitative data were described as number and percentage and were analysed by Chi-square test. Descriptive statistics of the quantitative data were done using Student's "t" test if normally distributed or

Table 1 Demographic data of the studied autistic patients ($n=50$)

Age (years)	Mean ± SD	5.58 ± 1.29
	Median	5.5
	Range	(3–8.5)
Sex	Males	40 (80%)
	Females	10 (20%)

Table 2 Volumetric analysis of the ventral diencephalon of the autistic patients ($n=50$)

Absolute total volume of VD (cm^3)	Mean ± SD	7.63 ± 0.79
	Median	7.41
	IQR	(7.015–8.32)
Absolute volume of right VD (cm^3)	Mean ± SD	3.78 ± 0.38
	Median	3.68
	IQR	(3.49–4.12)
Absolute volume of left VD (cm^3)	Mean ± SD	3.85 ± 0.41
	Median	3.74
	IQR	(3.51–4.2)
Relative volume of VD (in relation to ICV)	Mean ± SD	0.58 ± 0.04
	Median	0.59
	IQR	(0.542–0.614)

Mann–Whitney U test, and Kruskal–Wallis test if not normally distributed. The accepted level of significance in this work was started at 0.05. ($P<0.05$ was considered significant.)

Results

This study was carried out on fifty autistic children, 40 (80%) males and 10 (20%) females. The mean age of all patients was 5.58 ± 1.29 (range was 3–8.5) (Table 1).

There were 48 out of 50 children who demonstrated abnormal small ventral diencephalon volume, notably the relative volume which was found below the normal limits compared with normalized reference volume in function of sex and age (mean was 0.58 ± 0.04, and inter-quartile range was 0.542–0.614) (Table 2) (Figs. 2 and 3).

All cases were normocephalic; they demonstrated normal intra-cranial cavity volumes, and no case was categorized as micro- or macro-cephalic. Forty out of fifty cases showed increased total volume of grey matter (mean was 60.19, and inter-quartile range was 59.08–61.19), and eighteen out of fifty cases showed increased total volume of white matter (mean was 30.27, and inter-quartile range was 28.005–31.80). Regarding the major limbic system structures (amygdala and hippocampus), there were only two cases (4%) which showed increased relative volume of the total amygdala above the upper normal limits in relation to the intra-cranial cavity volume (mean was 0.142, and inter-quartile range was 0.136–0.15), whereas the remaining cases showed normal values. In addition, there were two other cases (4%) which demonstrated increased relative volume of the total hippocampus in relation to the intra-cranial volume above the upper normal limits (mean was 0.565, and inter-quartile range was 0.546–0.589), and the remaining cases showed normal relative volumes (Tables 3 and 4) (Figs. 4 and 5).

Comparison between the autistic patients and normal references revealed a significant differences regarding the VD volume and total volume of grey matter (P value was <0.001), whereas no significant differences were found regarding the white matter amygdala, hippocampus, basal ganglia, thalamus and cerebellum (Table 4).

The per cent agreement in the study was excellent between the readers, and the inter-reader reliability (IRR) was calculated at 98% for the presence or absence of structural brain anomalies. The IRR was non-applicable regarding the results of vol2Brain charts, as the process was fully automated and depended on a standardized screenshots of selected images.

Discussion

No single pattern of structural brain abnormality was found to be characteristic to ASD patients. Many studies have evaluated the role of volumetric brain MRI in assessment of region-specific structural changes such as grey and white matter volumes, in addition to subcortical structures which include the hippocampus and amygdala. The majority of studies have yielded conflicting results which varied from increased to decreased and even preserved volumes [8–10].

The current study has investigated the volume of ventral diencephalon which is believed to play a role in pathophysiology of ASD due to hypothalamic implication in socio-emotional and affiliative behaviour in humans.

The main finding in the current study was the consistent relation between ASD children and small volume of VD that was found in 48 out of 50 cases; this consistent feature appeared to be in the same line with the theory of endocrine functional alteration which suggests the presence of abnormal hypothalamic hormonal function in ASD patients including oxytocin hormone and other hypothalamic-related neuropeptides. There is a paucity of reports regarding the volumetric study of VD or its components in ASD. Kurth et al. [11] investigated the grey matter differences in fifty-two ASD children and fifty-two matched control subjects using brain MRI with voxel-based morphology analysis; they found significantly lower volume of hypothalamic grey matter in ASD cases compared with control subjects at the location of supraoptic and paraventricular nuclei of the hypothalamus ($T=5.24$, $P=0.017$ (FEW corr.), $Z=4.91$, $kE=13$). This finding could be in agreement with what the current study reported; although our study utilized

Structure segmentation

Subcortical	Total (cm^3/%)	Right (cm^3/%)	Left (cm^3/%)	Asymmetry (%)
Amygdala	2.04 (0.149)	1.01 (0.073)	1.03 (0.075)	-2.3810
	[0.105, 0.166]	[0.052, 0.083]	[0.052, 0.085]	[-17.037, 13.963]
Basal Forebrain	0.95 (0.069)	0.50 (0.036)	0.45 (0.033)	9.5238
	[0.039, 0.072]	[0.019, 0.037]	[0.018, 0.037]	[-40.071, 32.313]
Caudate	8.55 (0.622)	4.37 (0.318)	4.18 (0.304)	4.5648
	[0.486, 0.722]	[0.242, 0.359]	[0.242, 0.364]	[-10.192, 7.178]
Hippocampus	8.38 (0.610)	4.26 (0.310)	4.12 (0.300)	3.4465
	[0.412, 0.623]	[0.199, 0.313]	[0.208, 0.315]	[-13.855, 9.507]
Pallidum	2.64 (0.192)	1.31 (0.096)	1.32 (0.096)	-0.6504
	[0.182, 0.271]	[0.090, 0.135]	[0.091, 0.137]	[-14.759, 9.811]
Putamen	8.81 (0.641)	4.39 (0.319)	4.42 (0.322)	-0.8118
	[0.613, 0.859]	[0.303, 0.425]	[0.307, 0.436]	[-10.498, 6.549]
Thalamus	12.08 (0.879)	6.14 (0.446)	5.94 (0.432)	3.2317
	[0.777, 1.033]	[0.383, 0.510]	[0.391, 0.526]	[-10.070, 4.268]
Ventral DC	7.02 (0.511)	3.44 (0.250)	3.58 (0.261)	-4.0102
	[0.642, 0.825]	[0.312, 0.407]	[0.328, 0.420]	[-9.003, 0.948]

**All the volumes are presented in absolute value (measured in cm^3) and in relative value (measured in relation to the ICV).*

**The Asymmetry Index is calculated as the difference between right and left volumes divided by their mean (in percent).*

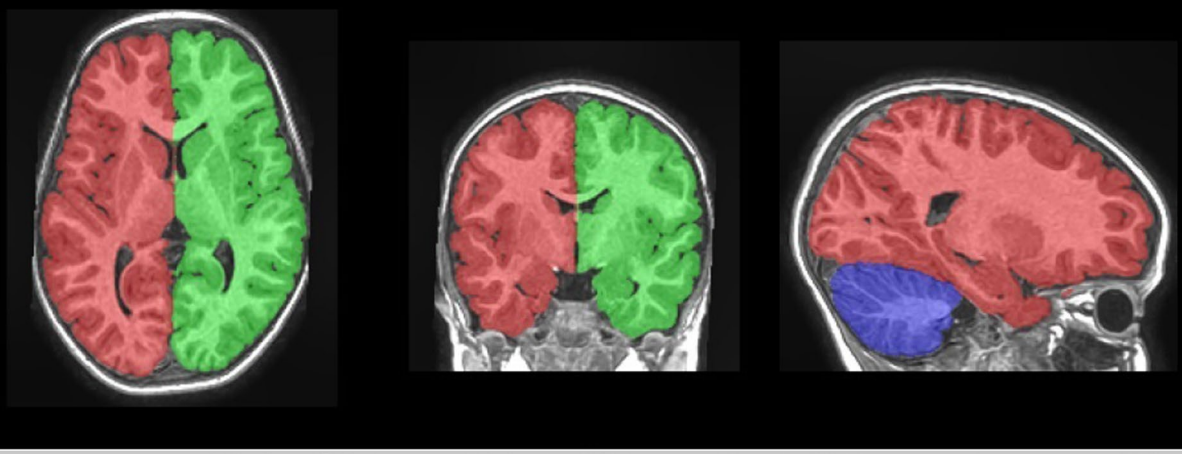
**Segmentation images are located in the MNI space (neurological orientation).*

**Values between brackets show expected limits (95%) of normalized volume in function of sex and age for each measure for reference purpose. Values outside the limits are highlighted in red.*

Fig. 2 Vol2Brain volumetry report of segmental subcortical structures in a 6-year-old male child with ASD showed reduced relative volume of ventral diencephalon (highlighted in red)

a different MRI brain volumetry system which did not differentiate between the hypothalamic nuclei and other VD components, the authors did not consider this point as an obstacle or limitation in our study due to universal methodological and technical difficulties regarding volumetric brain analysis in ventral diencephalon region. In another study in the same line, Wolfe et al. [12] examined the hypothalamic atrophy in ASD directly by measuring the grey matter density using voxel-based morphometry analysis on 3D brain MRI, and indirectly by measuring the third ventricular volume being surrounded by hypothalamic nuclei; they reported a decrease in hypothalamic grey matter density and an increase in third ventricle volume in ASD patients compared with typically developing individuals. To the best of the author's knowledge, no report has yielded a different finding [11, 12].

Macrostructures



Structure	Total (cm^3/%)	Right (cm^3/%)	Left (cm^3/%)	Asymmetry (%)
Cerebrum	962.75 (80.935)	482.18 (40.535)	480.57 (40.400)	0.3334
	[77.097, 86.150]	[38.487, 43.079]	[38.544, 43.137]	[-2.210, 1.918]
Cerebrum WM	346.40 (29.121)	173.37 (14.575)	173.03 (14.546)	0.1960
	[28.358, 38.439]	[14.169, 19.223]	[14.171, 19.234]	[-2.414, 2.519]
Cerebrum GM	616.35 (51.814)	308.81 (25.960)	307.54 (25.854)	0.4107
	[44.533, 51.916]	[22.229, 25.945]	[22.278, 25.998]	[-2.385, 1.873]
Cerebellum *	118.72 (9.980)	59.60 (5.010)	59.12 (4.970)	0.8097
	[8.122, 11.002]	[4.076, 5.520]	[4.037, 5.491]	[-2.819, 4.150]
Cerebellum WM	20.81 (1.749)	10.48 (0.881)	10.33 (0.868)	1.4712
	[1.541, 2.753]	[0.771, 1.398]	[0.765, 1.360]	[-3.916, 8.634]
Cerebellum GM	105.90 (8.903)	49.12 (4.129)	48.79 (4.102)	0.6691
	[6.729, 9.396]	[3.093, 4.334]	[3.079, 4.322]	[-4.000, 4.533]
Vermis	7.99 (0.672)			
Brainstem	13.54 (1.119)			
	[1.147, 1.579]			

**Cerebellum volumes does not include vermis volume.*

Fig. 3 Column chart of relative volume of ventral diencephalon (red column) among all fifty cases in relation to the upper normal (green column) and lower normal (blue column) limits

Regarding the increased volume of total grey matter in ASD in the current study, this could be in partial agreement with Kurth et al. [11] who investigated the grey matter difference in autism spectrum disorder, using voxel-based morphometry analysis in 52 affected children and adolescents, they observed a slightly higher global volume of the whole-brain grey matter in autism; however, the differences did not reach significance [11].

Regarding the amygdala and hippocampal volume changes in the current study, 96% of subjects showed no volume changes; this could be in agreement with Palmen et al. [13] who investigated the amygdala and hippocampus volumes in 42 medication-naive children with high-functioning autism and Asperger's syndrome on whole-brain MRI scans; they found no significant differences in amygdala and hippocampus volume for autistic and control subjects. In the same line, Barnea-Goraly et al. [14] investigated twenty-three children with autism with magnetic resonance imaging; they found preliminary evidence of normalization of amygdala volumes in

Table 3 Volumetric analysis of intra-cranial cavity, major limbic system and other structures in autistic patients ($n=50$)

Variable	Median (IQR)
Intra-cranial cavity volume (cm^3)	1329.5 (1234.9–1396.1)
Total absolute volume of amygdala (cm^3)	1.84 (1.69–2.03)
Right absolute volume of amygdala (cm^3)	0.96 (0.865–1.045)
Left absolute volume of amygdala (cm^3)	0.9 (0.825–1.01)
Relative total volume of amygdala (in relation to ICV)	0.142 (0.136–0.15)
Total absolute volume of hippocampus (cm^3)	7.23 (6.885–7.925)
Right absolute volume of hippocampus (cm^3)	3.61 (3.51–4.0)
Left absolute volume of hippocampus (cm^3)	3.69 (3.36–3.93)
Relative volume of hippocampus (in relation to ICV)	0.565 (0.546–0.589)
Total grey matter volume (cm^3)	60.19 (59.08–61.19)
Total white matter volume (cm^3)	30.27 (28.005–31.80)
CSF (cm^3)	7.63 (7.25–10.27)
Cerebellum (cm^3)	9.46 (9.23–9.86)
Vermis (cm^3)	0.68 (0.66–0.72)
Brain stem (cm^3)	1.14 (1.09–1.26)
Putamen (cm^3)	0.706 (0.683–0.720)
Caudate (cm^3)	0.639 (0.621–0.684)
Pallidum (cm^3)	0.222 (0.205–0.236)
Thalamus (cm^3)	0.873 (0.936–0.965)

ASD; however, they reported a significant increase in right hippocampal volume in the autism. On the other hand, several studies have yielded contradictory results; some of them found an association of ASD with volume increase in amygdala and/or hippocampus; these included Zhu et al. [15] who examined the amygdala volume in 39 preschool children with autism spectrum disorder and found significant high total volumes of the amygdala in the autism ($t=5.901$, $P<0.001$). Similarly, Gibbard et al. [16] investigated the amygdala volume and amygdala-cortical connections with ASD behaviours; they reported greater amygdala volume in ASD ($F(1,94)=4.19$; $P=0.04$) and altered microstructure of connections between the amygdala and the cortex. In contrast to all aforementioned studies, some other studies found significant correlation with volume reduction in the aforementioned structures such as Van Dessel et al. [17] who examined the amygdala in patients with attention-deficit/hyperactivity disorder; they suggested a functional significance of reduced amygdala volumes in attention-deficit/hyperactivity disorder. In another study, Nicolson et al. [18] studied the hippocampal abnormalities in autism using volumetric magnetic resonance imaging scan at 3 Tesla; they found subtle differences between patients and controls in right posterior hippocampus and suggested that autism might be associated with regional reductions in hippocampal size. These conflicting results along with the general lack of logic explanations of such volumetric abnormalities could raise more questions about the exact pathophysiology of medial temporal and global volumetric alterations in ASD population (13–18).

This study had some limitations: The first was the lack of control group of normal children of the same age; this was due to some logistic difficulties, as all of them would be young children and would be exposed to unjustified sedation, and the second was the relatively small sample size.

Conclusions

Based on the consistent significant volume decrease in the ventral diencephalon in patients with childhood autism, this study concluded that volumetric MRI analysis could be useful for diagnosis of childhood spectrum disorder and could be utilized as a reliable screening method in the clinically vague cases. Further study with a larger sample size including more age groups is recommended for more validation of the results.

Table 4 Comparison between autistic patients and the normal reference regarding VD, limbic and basal ganglia structures, total grey and white matters and cerebellum ($n=50$)

Variable	Autistic patients	Normal reference	*P* value
Abnormal (small) VD	48 (96%)	0 (0%)	< 0.0001
Abnormal (enlarged) Amygdala	2 (4.0%)	0 (0%)	0.31
Abnormal (enlarged) hippocampus	2 (4.0%)	0 (0%)	0.31
Abnormal (enlarged) caudate	2 (4%)	0 (0%)	0.317
Abnormal (small) pallidum	2 (4%)	0 (0%)	0.317
Abnormal (small) thalamus	2 (4%)	0 (0%)	0.317
Abnormal (enlarged) total grey matter volume	40 (80%)	0 (0%)	< 0.001
Abnormal (small) total white matter volume	18 (36%)	0 (0%)	0.05
Abnormal (small) cerebellum	4 (8%)	0 (0%)	0.153

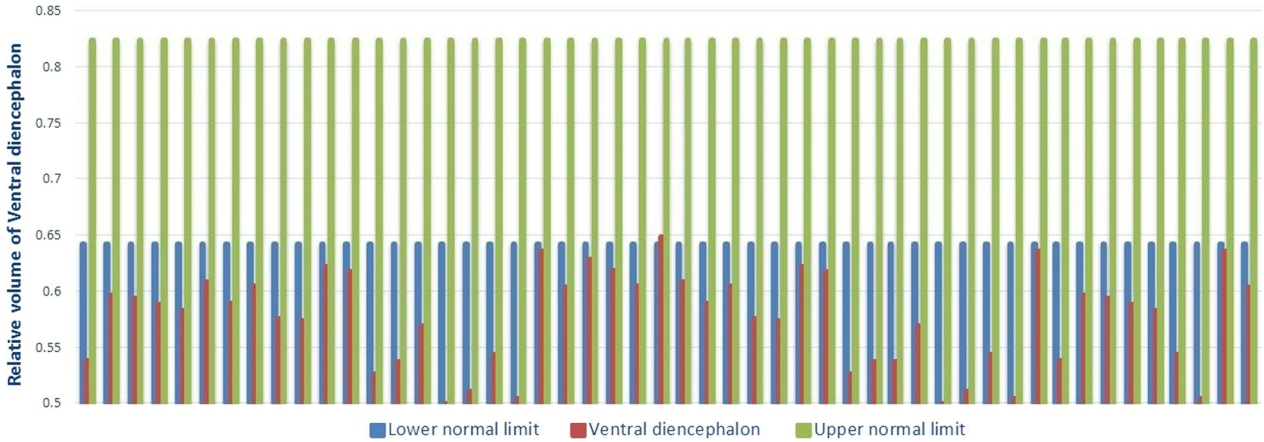


Fig. 4 Vol2Brain volumetry report of brain macro-structures in a 7-year-old male child with ASD showed increased volume of the cerebral grey matter and reduced volume of the brain stem

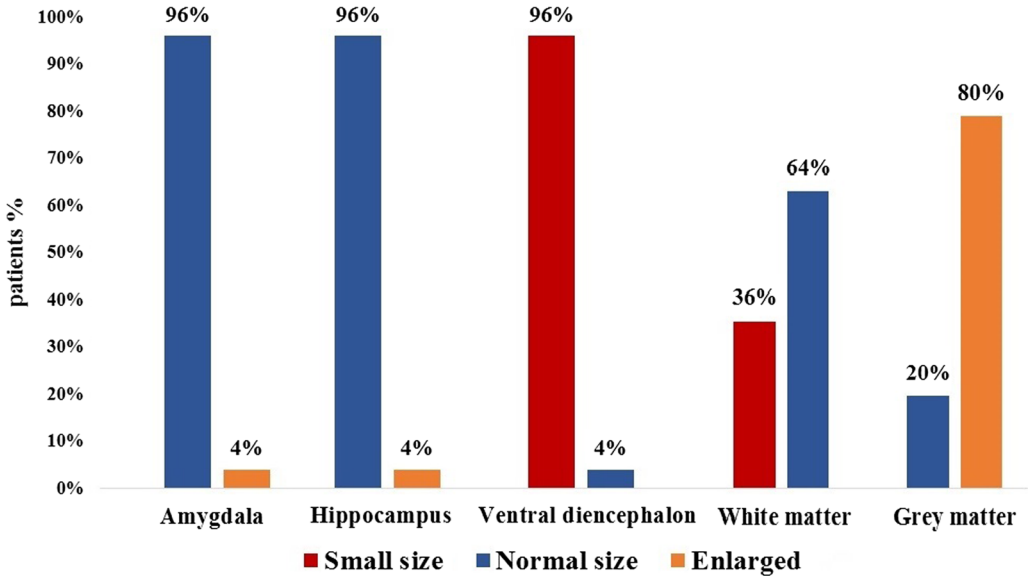


Fig. 5 Column chart of percentage of abnormal values of limbic system structures, ventral diencephalon and white and grey matters

Abbreviations

ASD Autism spectrum disorder
ICV Intra-cranial cavity volume
MRI Magnetic resonance imaging
VD Ventral diencephalon

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Not applicable.

Author contributions
TEl carried out imaging reading and analysis, statistical analysis, in addition to editing of publications. HSA carried out the study design, as well as the supervision on editing of publications. SMM carried out all clinical issues of the patients including their examination and data collection. HAAM and ARI carried out data collection and contributed in publications editing. MFA carried out the study design, statistical analysis, as well as editing of publications/presentation. All authors read and approved the final manuscript.

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Availability of data and materials
The datasets used and analysed during the study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent for participates
The study was approved by the Research Ethics Committee of the Faculty of Medicine, Minia University, on 22 March 2021; reference number of approval: 16:3/2021. All cases gave written informed consent to participate in the research.

Consent for publication
All patients included in this study gave written informed consent for data publishing contained within this study.

Competing interests
The authors declare that they have no competing interests.

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