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Brain volumetric MRI study in healthy adolescent and young person's using automated method

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ABSTRACT

Objective: Adolescence is a critical period for the maturation of neurobiological processes that underlie higher cognitive functions and social and emotional behaviour. However, there are limited studies that investigated brain volumes in healthy adolescents and young persons. The aim of this study was to compare the Grey Matter (GM), White Matter (WM) and some specific brain subcortical volumes such as hippocampus and amygdala between healthy adolescents and young groups by using VolBrain.

Material and Methods: Magnetic resonance imaging brain scans were retrospectively obtained from 20 healthy adolescent and young subjects. The mean ages of the adolescent and young persons were 13±1 and 24±2, respectively. Brain parenchyma (BP), GM, WM and asymmetry features were calculated using VolBrain, and the GM and WM volumes of each subjects were compared with those of the both groups. The current study to examine whether regional gray matter (GM), white matter (WM), cerebrospinal fluid (CSF), some brain subcortical structures volumes differed between healthy adolescent and young groups. Also, of the whole brain, hemispheres, and hippocampus, amigdala of adolescent and young subject volumes were measured with an automated method.

Results: We have observed that the young group was found to have a 4 % less in volume of GM, when compared with adolescent groups.

Conclusion: Our data indicate that quantitative structural Magnetic Resonance Imaging (MRI) data of the adolescent brain is important in understanding the age-related human morphological changes.

Keywords: Adolescence, Brain volume, Gray Matter (GM), White Matter (WM), VolBrain

INTRODUCTION

Adolescence is a critical period for psychological and social development. Second decade of life includes concurrent pubertal changes and sex-based vulnerabilities (**1, 2**). This is a period of physical and cognitive development that finds their identity and learns the mechanisms of adult personal relationships to cope with various problem behaviours. However, adolescence is a critical period for maturation of neurobiological processes that underlie higher cognitive functions and social and emotional behaviour (**3**) making these individuals under the risk of the development of major depressive disorder (MDD) that is a leading cause of inability worldwide with the peak period of onset occurring during adolescence (**4**).

In the early postnatal period the number of synapses in the brain, axonal and dendritic branches, together with myelination increase due to an extreme upsurge of brain volume. Studies have already revealed that brain volume shows a roughly linear increase in the White Matter (WM) volumes during the first 25 years of life. In this regards, the development of WM and Grey Matter (GM) is associated with new connections among neurons, glial cells, and myelin (**5**). During adolescence, brain development characteristically shows significant reductions of cortical gray matter, together with an increase in white matter (**6-8**). For instance, Giedd et al. found an increase in white matter is linearly throughout the development, while gray matter surges at pre-adolescence peak in the frontal cortex during adolescence, and continues to decrease all through post-adolescence (**7**).

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It is known that cortical and global volumes reduce in a linear manner together with age, while the volume of cerebrospinal fluid (CSF) increases. Furthermore, it is recognized that mean total cerebral volume was approximately 10% larger in adult male subjects compared with adult females (9). During the adolescence period, hormonal and neurodevelopmental changes are mediated by the growth of neural processes, remodeling of synaptic connections, increased myelination in prefrontal areas, and maturation of connecting subcortical regions (10).

To the best of our knowledge, there are limited brain volumetric studies in adolescents that have only included some mood disorders (10-12). These studies have shown that, there are critical differences in hippocampus and amygdala volumes in different neurological and psychiatric disorders in adolescence, including schizophrenia, temporal lobe epilepsy, depression, and bipolar disorder (13). Considering all of these findings, we aimed to compare the GM, WM, and some specific brain subcortical volumes such as hippocampus and amygdala between healthy adolescents and young groups by using VolBrain.

MATERIALS and METHODS

Study Population and Design

Patients

A total of 20 healthy female and male patients were included in this study. The average age of the male (n=5) and female (n =5) in the adolescent grouping was 13±1.1 and 14 ±1.5, respectively. The average ages of the male (n=5) and female (n=5) of the young group were 25±1.8 and 24.4 ± 2.5 years, respectively. All subjects were right-handed and healthy without known neurological or psychological disorders. No significant age variations between males and females were present in either of the groups.

This study was performed at the Radiology and Anatomy Departments in Alanya Alaaddin Keykubat University, Alanya Training and Research Hospital. Informed consent form (written) were supplied by their surrogates' for all patients. This study was approved by the local ethics committee of scientific researches of Alanya Alaaddin Keykubat University Faculty of Medicine (Ethics committee decision number: 2018/3)

Neuroimaging

Neuroimaging was performed using a 1.5 T MRI device (GE, SIGNA Explorer, General Electric, Mildwaukee, US). Structural images were acquired using 3D T1 fast spoiled gradient recalled acquisition in the steady state (FSPGR) sequence in the sagittal plane, using these parameters: TE= 1,7 msec, TR=5,95 msec, flip angle=12º, acquisition matrix= 256 x 256, FOV=256 mm2, number of slices=170 and slice thickness=1.0 mm.

VolBrain (https://volbrain.upv.es/ is a web based calculation of volume aiming to provide automatic analysis of MRI brain data. VolBrain operates as a black box solution obtaining anonymized MRI brain volumes in NIFTI format and then produces a report in pdf format including the volumes of the main IntraCranial Cavity (ICC) tissues (i.e., CSF, WM and GM), also providing volume data of macroscopic areas including cerebellum, brain hemisphere, and brainstem. Furthermore, automatic subcortical structure segmentation is achieved, and the associated label maps and volumes are delivered. The whole process takes average 12 min. But, the scan time can vary due to the amount of jobs lined up on the web-server. The following figure briefly outlines the process (14). The results can downloadable as PDF file (**Figure 1, Figure 2**). We calculated volumes of CSF, WM, GM, brain hemispheres, cerebellum, and brainstem using volBrain pipeline, **Figure 1 and Figure 2**.

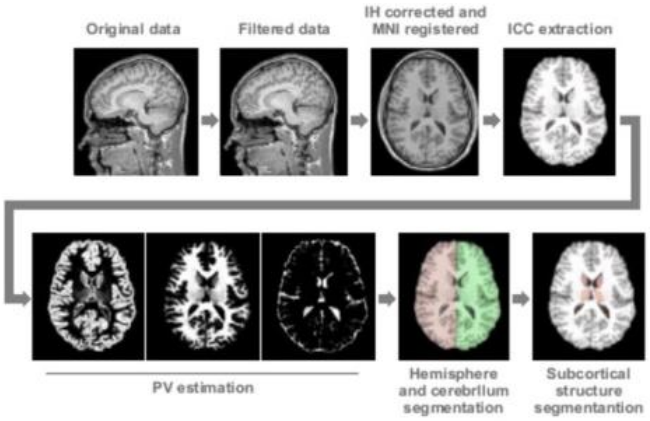
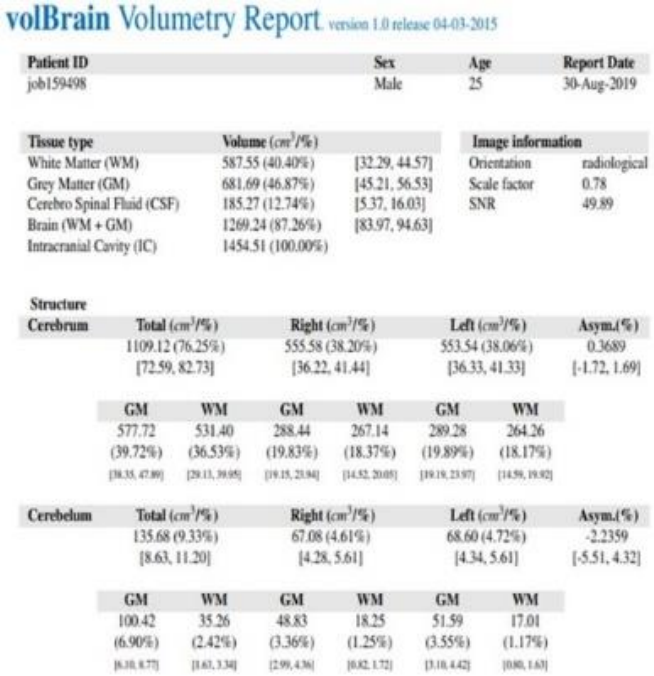


Figure 1: Example of automatic subcortical structure segmentation via VolBrain (http://volbrain.upv.es/)



volBrain Volumetry Report version 1.0 release 04-03-2015

Patient ID	Sex	Age	Report Date
job159498	Male	25	30-Aug-2019

Tissue type	Volume (cm^3/%)		Image information	
White Matter (WM)	587.55 (40.40%)	[32.29, 44.57]	Orientation	radiological
Grey Matter (GM)	681.69 (46.87%)	[45.21, 56.53]	Scale factor	0.78
Cerebro Spinal Fluid (CSF)	185.27 (12.74%)	[5.37, 16.03]	SNR	49.89
Brain (WM + GM)	1269.24 (87.26%)	[83.97, 94.63]		
Intracranial Cavity (IC)	1454.51 (100.00%)			

Structure						
Cerebrum	Total (cm^3/%)		Right (cm^3/%)		Left (cm^3/%)	Asym.(%)
	1109.12 (76.25%)		555.58 (38.20%)		553.54 (38.06%)	0.3689
	[72.59, 82.73]		[36.22, 41.44]		[36.33, 41.33]	[-1.72, 1.69]
GM	WM	GM	WM	GM	WM	
577.72	531.40	288.44	267.14	289.28	264.26	
(39.72%)	(36.53%)	(19.83%)	(18.37%)	(19.89%)	(18.17%)	
[38.35, 47.89]	[29.13, 39.95]	[19.15, 23.84]	[14.52, 20.05]	[19.19, 23.97]	[14.59, 19.92]	
Cerebelum	Total (cm^3/%)		Right (cm^3/%)		Left (cm^3/%)	Asym.(%)
	135.68 (9.33%)		67.08 (4.61%)		68.60 (4.72%)	-2.2359
	[8.63, 11.20]		[4.28, 5.61]		[4.34, 5.61]	[-5.51, 4.32]
GM	WM	GM	WM	GM	WM	
100.42	35.26	48.83	18.25	51.59	17.01	
(6.90%)	(2.42%)	(3.36%)	(1.25%)	(3.55%)	(1.17%)	
[6.10, 8.77]	[1.63, 3.34]	[2.99, 4.36]	[0.82, 1.72]	[3.18, 4.42]	[0.80, 1.63]	

Figure 2: VolBrain PDF result.

We downloaded MR T1 data from the scanner, transferred and processed using different softwares. We saved MR images as niftii format. For this purpose, we used personal computer on a 32-bit Dell PC, running Windows 10 operating system. We used volBrain to calculate volume. Using the volBrain (http://volbrain.upv.es/) pipeline does not require any installation, configuration or training. The volBrain volumetric analysis system works remotely through a web interface using a SaaS (Software as a Service) model to automatically provide a report containing volumetric information from any submitted case. Data analysis focused on volume (cm^3) in some regions in the brain: GM and WM

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of the cerebral cortex and total brain. The Asymmetry Index is calculated as the difference between right and left volumes divided by their mean (in percent) (**15, 16**).

Asymmetry index is calculated by

(left volumes-right volumes)/mean (left volumes, right volumes) × 100% Eq.1

Statistical Analysis

All statistical analyses were performed with the SPSS software package. The whole-brain volume analysis was performed with two-way analysis of variance (ANOVA) where, the two factors was sex and age.

The coefficient variation (CV) for the whole-brain volume, right and left hemisphere, in both adolescent and young groups, were calculated as the standard deviation of the volume and then divided by mean volume. Statistical significance tests were evaluated at a level of significance of 0.05.

RESULTS

The average brain volume was 1356,02±106,04 cm^3 for young female, 1290,20±100,54 cm3 for young male, 1276,17±106,44 cm^3 for adolescence female, and 1390,50±57,784 cm^3 for adolescence male.

Table 2 and 3 presents adult and adolescents' comparisons for average and relative volume of WM, GM, and CSF. Volumetric analyses showed that the young group had less GM volume than the adolescence group.

According to average GM volume measurements, approximately 4% volume loss from adolescent to young participants has been observed (**Table 2**). No significant variance was found between sex and age for brain volume.

Figure 3 displays the change in volume in the right and left hemispheres for adolescence and young female, and male participants (**Figure 3**).

Combining the data from the female and male subjects, young male subjects were found to have 1% volume forfeiture in the right hemisphere and 2% volume forfeiture in the left hemisphere for GM. Moreover, male subjects showed higher left or right hemisphere volume, than females in adolescence and young participants.

Right and left hemisphere volume was similar in young and adolescent participants. Detailed hemisphere volume and relative values are provided in **Table 3, 4**.

We found that there was a significant group–sex effect on WM volume using two-way ANOVA. This indicates that group-related brain volume depended on sex. But, no significant group–sex effect on GM volume using two-way ANOVA was found, indicating that group brain volumes were not dependent on sex (**Table 5, 6**). CV volume values in adolescent and young groups were between 2 and 12%.

Table 7 shows the descriptive statistics for adolescent and young groups in subcortical structures asymmetry. Although, the Amigdala has negative asymmetry among the age related groups , the statistically important difference was not found.

We found that the young group had slightly less caudate, thalamus and globus pallidus volumes than adolescence group. But, there were no statistically important differences between groups for subcortical structures volumes (p>0.05) (**Table 8**).

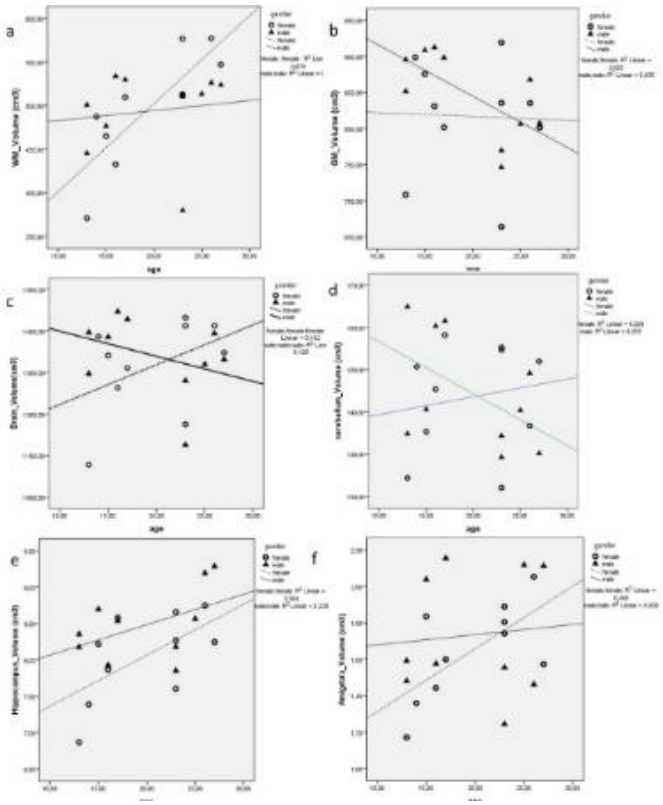

Figure 3: Scatterplots of 20 healthy subjects with absolute WM, GM, brain, cerebral asymmetry, cerebellum, hippocampus, and amygdala volumes shown as a function of age (a-f).

Table 1. Average volume of Brain, GM, WM, CSF (cm^3).

	WM	GM	CSF	Brain
Adolesence				
Female	453.19±48.41	822.98±66.73	150.12±31.36	1276.17±106.44
Male	497.38±37.24	893.11±24.31	136.58±44.26	1390.50±57.784
Young				
Female	545.16±32.47	810.86±93.16	132.24±28.17	1356.02±106.04
Male	490.76±62.43	799.43±46.12	189.12±63.72	1290.20±100.54

Note: Value represents means ± standard deviations.

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Table 2. The relative volume of Brain, GM, WM, CSF (%)

	WM	GM	Brain Tissue
Adolesence			
female	31.75±2.00	57.72±1.46	10.52±1.93
male	32.56±0.72	58.62±2.61	8.82±2.40
Young			
female	36.78±2.80	54.39±2.32	8.83±1.34
male	33.14±2.66	54.23±2.80	12.63±3.36

Value represents means ± standard deviations

Table 3. Hemisphere volume values (cm^3)

	Cerebrum Right	Cerebrum Right GM	Cerebrum Right WM	Cerebrum Left	Cerebrum Left GM	Cerebrum Left WM
Adolescence						
Female	556.57±48.4	350.67±30.8	205.90±21.9	554.37±48.3	350.82±31.5	203.54±21.3
Male	607.52±24.7	381.83±10.6	225.69±16.9	606.68±21.3	382.63±9.60	224.05±16.3
Young						
Female	593.98±45.6	346.16±39.76	247.82±15.5	593.37±47.1	347.65±39.625	245.72±16.14
Male	565.23±47.5	342.82±21.5	222.41±28.7	565.31±46	342.07±19.44	223.23±30.4

Table 4. The relative volume of hemisphere (%)

	Cerebrum Right	Cerebrum R GM	Cerebrum R WM	Cerebrum Left	Cerebrum L GM	Cerebrum L WM
Adolesence						
Female	39.01±0.75	24.58±0.7	14.42±0.87	38.86±0.8	24.60±0.86	14.26±0.84
Male	39.84±1.12	25.07±1.2	14.77±0.25	39.80±1.3	25.13±1.4	14.67±0.36
Young						
Female	39.94±0.43	23.22±0.9	16.72±1.31	39.89±0.3	23.32±0.9	16.57±1.21
Male	38.25±1.32	23.24±0.9	15.01±1.18	38.27±1.5	23.20±1.1	15.07±1.42

Table 5. Two way ANOVA of WM volume

	Df	SS	MS	F	P
Group	1	9104.58	9104.68	3.924	0.065
Sex	1	129.978	129.978	0.056	0.816
Group X sex	1	12149.87	12149.87	5.243	0.036*
Residual	16	37076.29	2317.26		
Total	19	58460.82	3076.88		

Table 6. Two way ANOVA of GM volume

	Df	SS	MS	F	p
Group	1	13988.35	13988.35	3.298	0.088
Sex	1	430.07	430.07	1.016	0.329
GroupXsex	1	8314.51	8314.51	1.960	0.181
Residual	16	678.5991	4241.25		
Total	19	94470.17	4972.11		

Table 7. Subcortical structures asymmetry for Adolescent and Young groups

	Adolescence				Young			
	Female		Male		Female		Male	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Caudate	-0,41	1,90	3,85	3,29	3,51	2,98	-0,74	3,65
Putamen	-2,50	1,83	-0,66	2,67	-3,31	1,22	-2,12	2,06
Globus Pallidus	3,40	2,53	3,43	5,46	0,67	6,60	0,46	9,11
Thalamus	-2,35	3,38	-0,14	5,07	-0,68	3,32	1,51	5,11
Hippocampus	-5,58	7,41	-0,83	4,69	1,95	5,01	-2,89	3,34
Amigdala	-8,79	10,17	0,60	17,93	1,58	5,64	-11,69	19,43

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Tablo 8. Average subcortical structures (cm^3).

	Caudate		Thalamus		Globus Pallidus		Hipocampus		Amygdala	
Subject	**A**	**Y**	**A**	**Y**	**A**	**Y**	**A**	**Y**	**A**	**Y**
1	9,55	8,40	14,03	14,04	2,54	2,53	7,39	8,27	1,36	1,80
2	6,51	8,30	11,76	13,34	2,02	2,71	6,87	8,75	1,17	2,05
3	8,88	7,90	11,41	11,70	2,29	2,46	7,87	7,60	1,44	1,89
4	8,45	9,74	12,83	13,53	2,67	2,52	8,22	8,66	1,83	1,74
5	8,37	7,10	14,49	12,92	3,02	2,28	8,58	8,24	1,60	1,57
6	8,00	7,71	12,03	11,78	2,18	2,03	8,70	7,85	2,04	1,24
7	8,06	7,62	13,00	11,22	2,59	2,56	8,35	9,19	1,59	1,46
8	8,70	8,76	14,24	12,41	2,61	2,44	8,54	8,56	2,16	2,12
9	9,59	7,48	13,83	12,59	2,89	2,31	8,18	8,18	1,48	1,55
10	9,22	9,00	13,31	12,33	2,71	2,73	7,93	9,29	1,58	2,11
Mean	**8,53**	**8,20**	**13,09**	**12,59**	**2,55**	**2,46**	**8,06**	**8,46**	**1,63**	**1,76**
St.Dev	**0,91**	**0,80**	**1,08**	**0,89**	**0,31**	**0,21**	**0,57**	**0,54**	**0,30**	**0,30**

A: Adolescence, Y: Young

DISCUSSION

Advances in neuroimaging techniques have enabled us to study the human brain in new ways. Particularly, magnetic resonance imaging (MRI) could provide unparalleled investigation of brain structure and function (**17, 18**). Most of the studies on functional or structural changes in the brain of adolescents with psychiatric disorders, are based on magnetic resonance imaging (**10**). However, no consistent results have been obtained from the few MRI studies of these brain regions in children and adolescents. Previous neuroimaging studies have performed into the development of GM, WM and frontal lobe in children and adolescents (**19, 20**). The adolescent brain also remains under development during this time. Adolescents often engage in increased risk-taking behaviours and experience heightened emotions during the puberty; this may be due to the fact that their frontal lobes—which are responsible for judgment, impulse control, and planning—are still maturing until the early adulthood (**21**).

Hariri et al. have shown that amplified prefrontal activity is related to heightened modulation of the amygdala response to angry and fearful faces stimuli (**22, 23**).

Accordingly, adolescents who continued their aggressive affective behaviour for a longer duration during a conflict episode with their parents were observed to have enlarged amygdala volumes (**24, 25**).

This is consistent with previous evidence suggesting that the amygdala plays a key role in aggressive behaviour and angering processing.

Also, an increased baseline of amygdala activity was observed in aggressive adult populations, while physical amygdala irregularities in adult psychopathologies were manifested by aggressive behaviour and impulsivity (**24, 25**). Hare et al. (**26**) suggested that an increased volume of the amygdala in adolescence may indicate to a predisposition towards a sustained experience of negative affect that could impair behavioural and cognitive regulation and thereby lead to aggressive behaviour. In line with this, Groen et al. (**27**) found that the right amygdala and left hippocampus were significantly enlarged in the autism compared with the control group while no significant correlations were observed between age and amygdala or the hippocampus volume.

These findings were confirmed by Blumberg et al. (**28**), which revealed that the amygdala and hippocampus were significantly smaller in the bipolar disorder compared with the control group. However, many of these studies had small sample sizes, potentially causing some inconsistencies in results (**29**). Indeed, through adolescence, the frontal gray matter volume visualized by a structural MRI was observed to shrink while white matter steadily rises (**10**).

The progression of white and gray matter in adolescent schizophrenia is retarded from adolescent controls and gradually deviates from normal control patients to follow a similar pattern to the irregular development of neuropathology in adult-onset schizophrenia (**30**). These studies finally indicated that longitudinal research is needed to establish whether a larger amygdala volume during early adolescence could produce a risk for the development of psychopathology and aggressive behaviour in adulthood (**25**). In our study, we found that adolescence group had slightly less amygdala volume than the young group. But, there were no statistically significant differences between the groups. It is difficult to estimate what caused to this inconsistency. However, it can be hypothesized that increases in the white matter might reflect, in part, increased myelination, which might lead to relative decreases in gray matter volumes. Accordingly, brain size during adolescence typically shows significant decreases in cortical gray matter and increases in white matter (**8, 31, 32**). Despite these findings, Giedd et al. (**19**) stated that frontal and temporal gray matter volumes peak between 11 to 16 years in girls and boys. Also, the dorsal lateral prefrontal cortex which is the latest brain region, start to mature in early of 20s. Thus, structural volumetric neuroimaging studies have stated that, even though global brain volume is established by early school-age (33), the transformation of white and grey matter happens during adolescence and remains open until early-adulthood (34). For instance, the hippocampus plays a very important role in cognitive development in children and adolescents (13), and white matter volume steadily increases during the adolescence (**19**). Also there have been many external factors (i.e., stroke, trauma) shown to increase the risk of the development of mood disorders connected with critical brain regions such as the hippocampus (**35-40**). Accordingly,

increased gray matter density of the hippocampus, amygdala, and the posterior temporal cortex have been already reported among the adolescence (**41, 42**). We found that there was approximately 4% volume loss in GM from adolescent to young participants volume while there was significant group–sex effect on WM volume by using two-way ANOVA, which could mean that group-related brain volume changes were sex-dependent. However, our results indicated that there were no statistically differences between groups for subcortical structures volumes. It has already been shown that there is total volume forfeiture with age, and cortical volumes reduce in a linear manner with age as the CSF volumes rise (**20**). Our results have the context of the following study limitations; first, our sample size is relatively small, and further investigations with a larger sample size might be needed to endorse the findings in this study. Second, we used automated segmentation procedures, and we did not compare manual tracing method although studies have shown that there are no significant differences between automated segmentation method and manual tracing of the brain subcortical volume in the literature (**43**).

CONCLUSIONS

As a conclusion, our present results suggest that quantitative structural MR data of the adolescent brain is vital in determining age-related human brain functioning, which could help in refining the clinical diagnosis of various psychiatric disorders characterized with brain volume loss.

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Ethical approval: The study was conducted according to the guidelines of the Declaration of Helsinki and approved by Local Ethical Committee.

Conflict of interest: The author declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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