Journal of Experimental and Clinical Medicine
https://dergipark.org.tr/omujecm

Research Article

J Exp Clin Med
2022; 39(4): 1217-1222
doi: 10.52142/omujecm.39.4.49

Sex and age-dependent changes of the cerebral cortex in young adult Sudanese: A brain segmentation study

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Received: 09.08.2022 • **Accepted/Published Online:** 17.09.2022 • **Final Version:** 29.10.2022

Abstract
The present study aimed to measure the cortical structures of cerebral hemispheres, including cortical thickness (CT), grey and white matter volume (GMV and WMV) and volume fraction (GMVF and WMVF), in addition to the volume (V) and cortical area pial (CAP) in normal young adult Sudanese and to investigate the effect of sex and age on these cortical structures. The study included 139 healthy young adult Sudanese subjects (80 males and 59 females). Participants' ages ranged from 20-40 years. T1-weighted MR brain images with a thickness of 1 mm were obtained. MR images of the subjects were analyzed using the automatic segmentation software (BrainSuite). Cortical structures of the cerebral hemispheres were estimated using the output data of the process of the software. Sex differences were noticed in the GMV ($325.76\pm38.74 cm^3$), WMV ($182.09\pm26.70 cm^3$), V ($507.85\pm62.20 cm^3$), and CAP ($1263.22\pm127.42 cm^2$) of the cerebral hemisphere ($P<0.05$). However, there were no differences between genders in CT (3.81±0.17mm), GMVF (64.20±1.98%), and WMVF (35.80±1.98%) of the cerebral hemisphere ($P>0.05$). Changes with age were seen in the GMV, GMVF, WMVF, and CAP of the cerebral hemisphere ($P<0.05$). However, there were no changes with age in CT, WMV, and V of the cerebral hemisphere ($P>0.05$). Sex and age are important factors to consider when evaluating the cortical structures of the cerebral hemisphere. Sex affects GMV, WMV, V, and CAP, but not on the CT, WMVF, and GMVF. Age affects GMV, CAP, WMVF, and GMVF, but not on the CT, V, and WMV.

Keywords: cortical thickness, volume fractions, cortical area, cerebral hemispheres, BrainSuite

1. Introduction

The cerebrum is the largest part of the brain, which consists of two hemispheres separated by a longitudinal fissure; the corpus callosum, which connects the two hemispheres, is located at the base of this fissure (1). The right and left hemispheres do tend to have specific specializations, with the left hemisphere, in particular, being devoted to language and memory and the interaction of language and memory. The right hemisphere is heavily involved in spatial cognition, which is our understanding of space around us; it also allows us to process music (2).

The cerebrum has an outer cortex consisting of grey matter (GM) and an inner core of white matter. The cortical layer is located between the pial or outer surface at the GM/CSF (cerebrospinal fluid) interface and the inner surface at the GM/WM (white matter) junction (3). Each surface unit of the cerebral cortex can be defined as topologically equivalent to a 3D sphere that assists in measuring its cortical structures such as thickness, volume, grey and white matter volume and cortical area pial (3).

It has been shown that various factors such as sex and age may influence these cortical structures in the normal human cerebrum. Knowledge and understanding of sex impact on the cortical structures are of significant importance to adequately address the sex differences in managing risk factors, symptoms, course of disease and treatment (4). Furthermore, age-associated changes in cortical structures in healthy adults have greater importance because the determinations of normal age-specific values in the brain have a role in evaluating both clinical-pathologic conditions and normal aging processes.

To our knowledge, no studies have been done to assess the effect of sex and age on all these cortical structures in healthy young adult subjects with no history of psychiatric and neurological diseases. These cortical structures were measured from T1 weighted magnetic resonance (MR) imagining by using automatic segmentation software called BrainSuite.

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2. Material and Methods

2.1. Subjects

139 Sudanese young adults in good health, between the ages of 20 and 40, participated in the current study. Age (males and females were 28.5.72 and 28.6.00 years old, respectively) and body mass index (BMI) (males and females were 23.933.6 and 24.895.07kg/cm^2, respectively) were matched between the sexes.

Participants who used drugs suffered from head trauma, neurological disorders, psychiatric disorders, or had a congenital brain deformity were excluded.

The Ethical Committee of the National Ribat University approved the study.

2.2. Magnetic resonance imaging

Three-dimensional T1-weighted MR brain pictures were acquired using a 1.5 Tesla Philips scanner, Version: 3.2.1, in 5 minutes and 18 seconds, with a slice distance of 1.0mm, a field of view of 250 read, 192mm phase, TR=1657ms, TE=2.95ms, bandwidth 180Hz/pixel, flip angle 15°, and ECHO spacing=7.5ms.

2.3. MR images analysis

BrainSuite software tools, which automatically process the MR image of the brain, were used to examine the MR images.

Surface and volume registration and cortical surface extraction sequence (CSE) are the two processes used by BrainSuite to evaluate MR images. These procedures take about three hours to complete.

2.4. Cortical surface extraction sequence (CSE)

The skull and scalp are stripped from the MR picture during this 30-minute stage, followed by correcting an error that occurred during the removal of the skull. Following a classification of the brain's tissue into white matter, grey matter, and cerebrospinal fluid, the program then divides the brain into its three main regions: the cerebrum, cerebellum, and brainstem. The mistake is fixed by removing the cortex from the affected brain hemisphere. Finally, the pial surface is generated, and each hemisphere's cortical surface is displayed in a separate hue (Fig.1.).

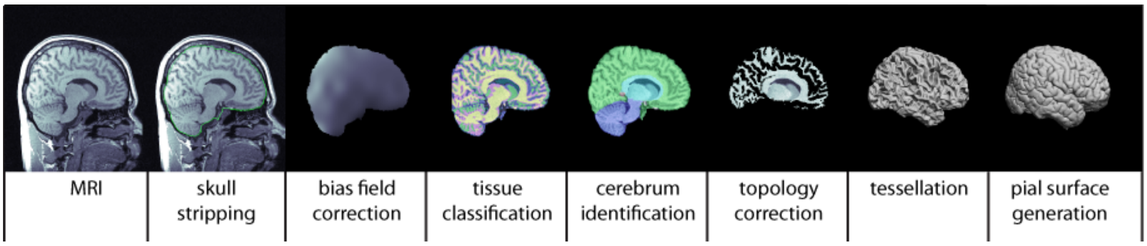

Fig. 1. Cortical surface extraction sequence (7)

2.5. Surface and volume registration (SVReg)

During this step, the cortical and subcortical structures are labelled, and the surfaces and volumes are registered to the brain atlas.

The output of BrainSuite in an excel sheet containing the measurement of each brain gyri such as grey matter volume, white matter volume, CSF volume, cortical area pial and midal and inner and cortical thickness (Fig. 2.).

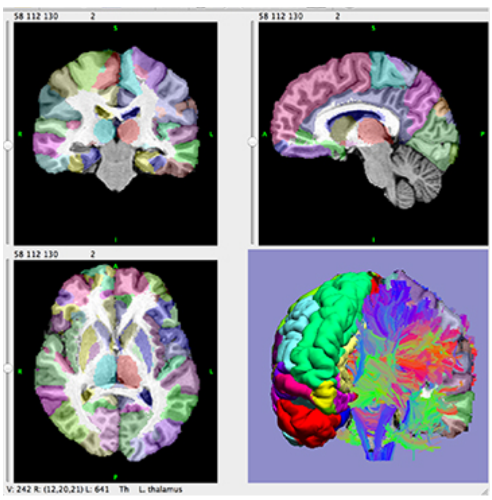

Fig. 2. MR image analyzed by BrainSuite (7)

BrainSuite automatically calculates cortical structures of the gyri of the cerebral hemispheres. The following formulas (1-5) were used in a Microsoft Excel worksheet to calculate cortical structures of the cerebral hemisphere.

2.6. Statistical analysis

Data were analyzed using Statistical Package of Social Science (SPSS) version 21.0. An Independent sample t.test was performed to compare mean values of grey and white matter between males and females. Bivariate correlation was used to evaluate the relationship between grey and white matter and age. P.value equal to or less than 0.05 was considered statistically different.

3. Results

There were no differences between genders in thickness, white and grey matter volume fraction of the right, left, and total cerebral hemispheres, and white matter volume of the left cerebral hemisphere. Conversely, gender differences were seen in the white matter volumes of the right and total cerebral hemispheres; grey matter volumes, volumes, and cortical areas pial of the right, left, and total cerebral hemispheres, which were larger in males than females ($P<0.05$).

The data details of the structures of the cerebral hemispheres are given in Table 1.

Table 1. Comparisons of structures of cerebral hemispheres between genders

	Right hemisphere		Left hemisphere		Total hemisphere	
Structures	Males	Females	Males	Females	Males	Females
Thickness (mm)	3.83±0.15	3.79±0.20	3.82±0.19	3.79±0.14	3.82±0.18	3.80±0.14
White Matter V (cm^3)	192.54±24.57	166.46±20.70*	186.32±28.76	177.81±24.20	664.69±82.76	633.68±66.30*
Grey Matter V (cm^3)	343.40±37.02	301.21±27.02*	332.84±40.88	316.81±33.16*	371.57±56.13	354.15±47.69*
Total V (cm^3)	535.93±57.96	467.68±44.02*	519.16±65.73	494.63±54.72*	1036.26±131.77	987.83±108.82*
Cortical AP (cm^2)	1327.86±118.25	1177.68±87.89*	1284.13±133.88	1232.74±107.69*	2570.57±272.64	2466.60±215.82*
White Matter VF (%)	35.89±1.93	35.55±1.94	35.82±2.21	35.88±1.79	35.80±2.08	35.79±1.75
Grey Matter VF (%)	64.11±1.93	64.45±1.94	64.18±2.21	64.12±1.79	64.20±2.08	64.21±1.75

(Mean±SD), V: volume, AP: area pial, VF: volume fraction, *: P≤0.05

3.1. Correlation between age and structures of the cerebral hemispheres

There was a negative correlation between age and cortical area pial, grey matter volume and volume fraction of the right cerebral hemisphere in males and females (Fig. 3, 4, 5) (P<0.05). Conversely, cortical areas pial, grey matter volumes and volume fractions of the left and total cerebral hemispheres were not correlated with age in males and females (P>0.05).

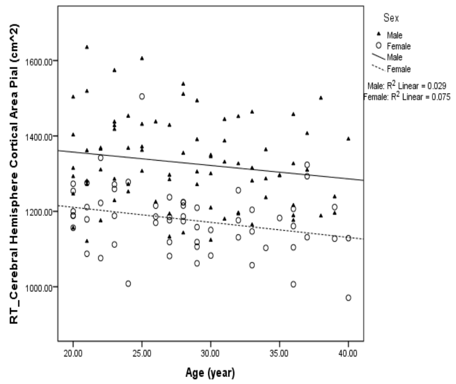

Fig. 3: Correlation between age and cortical area pial of right (RT) cerebral hemisphere

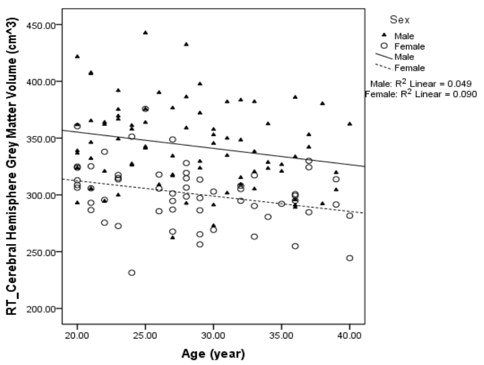

Fig. 4. Correlation between age and grey matter volume of right (RT) cerebral hemisphere

There was a positive correlation between age and white matter volume fraction of the right cerebral hemisphere in males and females (Fig. 6.) (P<0.05). Conversely, white matter volume fractions of the left and total cerebral hemispheres were not correlated with age in males and females (P>0.05).

There was no correlation between age and cortical thicknesses, white matter volumes, and volumes of the right, left, and total cerebral hemispheres in males and females (P>0.05).

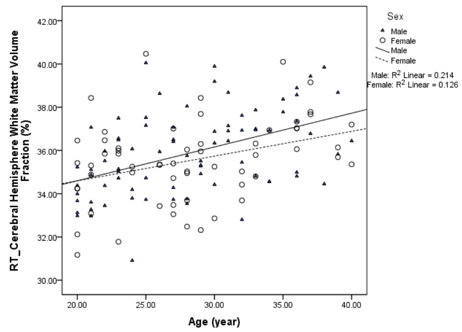

Fig. 5. Correlation between age and white matter volume fraction of right (RT) cerebral hemisphere

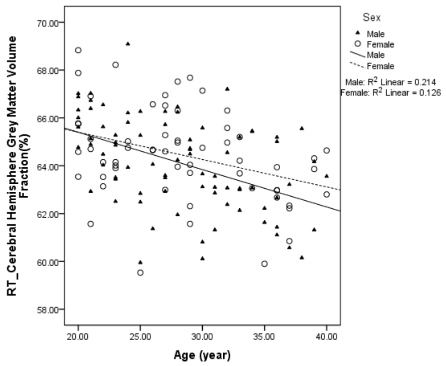

Fig. 6. Correlation between age and grey matter volume fraction of right (RT) cerebral hemisphere

4. Discussion

The present study's findings revealed no significant differences between genders in thickness, and grey and white matter volume fraction of the right, left, and total cerebral hemispheres.

The results about the cortical thickness confirmed the findings of other studies (6-8) and found that cortical thickness of the cerebral hemisphere is similar in males and females.

Results about sex differences in grey and white matter volume fractions of the cerebral hemisphere are inconsistent. The present findings are consistent with other studies which failed to detect significant sex differences in GM and WM volume fraction (9); and in contrast with previous studies, which detected higher GM volume fractions in females (10);

and others which revealed higher WM volume fraction in males (11). These conflicting results may be due to differences in methods used for obtaining tissue measurements.

The results of the present study revealed that after controlling age and BMI between genders, males had significantly larger white matter volumes of the right and total cerebral hemispheres; grey matter volumes, cortical volumes, and cortical areas pial of the right, left, and total cerebral hemispheres.

The present study's findings supported the findings of other studies, which found larger grey and white matter volumes in males (9, 12). In contrast, early studies initially found sex differences in white matter but not grey matter volumes (13, 14). The possible reasons for sex differences in grey and white matter volumes may be due to the impact of sex hormones. Recent findings have shown that there may be a connection between grey and whiter matter volumes and hormone levels of testosterone, estrogen, or progesterone (15). However, it is not yet fully understood how sex hormones lead to these differences (16).

Regarding the results of cortical volume, our results confirmed the previous studies and found larger volumes of the cerebral hemispheres in males (12, 17). An interesting result is a difference between males and females concerning the relationship between body size (height and weight) and cerebrum volumes. The current study found a significant strong positive correlation between males' weight/ height and cerebrum volume, but not for females. The present study outcomes suggest that in females, the factors that govern overall body growth (weight and height) are not closely related to or regulated by the factors that determine cerebrum growth. On the other hand, for males, there may be a modest relationship between overall body size (weight and height) and cerebrum size.

Is there any functional significance in the difference in the volume of the hemisphere between genders? Many scientists have thought over this question, but until now, there is no clear answer. Some scientists recognized a modest positive correlation between brain size and intelligence and reported that males are more intelligent than females (6, 18). Likewise, the relationship between intelligence and brain size cannot be defined as the bigger, the better; autism patients have larger brains when compared to healthy subjects (19).

Cortical volume is the product of grey and white matter volumes, so the observed differences in the volume between sexes are due to the sex differences in grey and white matter volumes. This study found a strong positive correlation between brain volume and grey and white matter volume in males and females.

Literature about sex differences in cortical area pial is not widely available. The previous studies confirmed our study and found that males had a larger cerebral hemisphere cortical surface area than females (20, 21). Sex differences in cortical volume could explain the sex differences in cortical area pial; the current study found a strong significant positive correlation between cortical volume and cortical area pial of the cerebral hemisphere. This result is consistent with a post-mortem study showing that a large cortex volume is mainly caused by a real expansion of cortical surface area (22).

The effects of aging on neuroanatomical structures have been studied using volumetric techniques such as region of interest (ROI) and voxel-based morphometric (VBM) analysis, and more recently through surface-based measures such as thickness and surface area. By applying an automatic segmentation tool (BrainSuite), the present study examined age-related structural changes upon several specific morphometric measures.

The present study found no correlation between age and cortical thickness, white matter volume and volume of the right, left and total cerebral hemispheres in males and females.

These results tally with the post-mortem and MRI studies which found that cortical volume of the cerebral hemisphere is stable between 20-50 years (23).

In contrast to the results of cortical thickness and volume, other MR imaging comprising 106 subjects ranging in age from 19 to 93 years found a negative correlation between age and thickness and volume of the right and left hemispheres (8). The possible reason for this inconsistency between the current and previous results may be related to the wide age range examined in the compared study. In contrast to the results of the white matter volume, other in-vivo studies have demonstrated that white matter volume increases until approximately the fifth decade of life and declines afterwards (24, 25).

The cortical structures which significantly change with age were cortical area pial, grey matter volume and volume fraction, and white matter volume fraction of the right hemisphere in males and females.

The finding of grey matter volume is confirmed by the in vivo studies that have shown that grey matter volume reduction begins in early adulthood and continues approximately linearly throughout adulthood (26, 27). The decrease in grey matter volume is due to degenerative changes that include loss of neurons (28) and dendritic arborization (29); and brain maturation changes which consists of synaptic pruning and myelination (30, 31).

The finding about cortical area pial is in agreement with the study that found reduction with age in cortical area pial of the cerebral hemisphere (32). A second study demonstrated that cortical surface area expanded until approximately 12.7 years and then shrank at a relatively modest rate until surface contraction became more pronounced after the age of 45 (33). The extent to which analogous cellular changes drive cortical area reduction in adulthood is unclear. Dendritic size and complexity loss could explain this reduction (34).

The present result also revealed that the grey matter volume fraction of the right cerebral hemisphere decreased with age, while the white matter volume fraction of the right cerebral hemisphere increased with age and coincidence to a decrease in grey matter volume fraction; these combination changes explain why cerebral volume stable between 20-40 years.

The strengths of the current study are the inclusion of a large sample and measuring the cortical structures by applying an automatic segmentation tool. A limitation of the present study is a cross-sectional study, which describes differences between subjects of different ages rather than describing changes correlated with age over time in individual subjects.

Age and gender both impact the cerebral hemisphere's structural makeup. The volume, grey and white matter volumes, and cortical area pial of the hemispheres were all considerably greater in males than in females, but the thickness and grey and white matter volume fractions were not statistically different. Only the right hemisphere's cortical area pial, white matter volume fraction, and grey matter volume and volume fraction all significantly changed with age; however, white matter thickness and volume and volume did not.

This study marks the first to offer baseline information on cerebral hemisphere cortical architecture. Compared to other normative studies or illness states, it can be utilized to identify considerable deviation from normal structural values.

Conflict of interest

The authors declared no conflict of interest.

Acknowledgments

This study was supported by Organization for Women in Science for Developing World (OWSD).

Authors' contributions

Concept: W.A., T.O., A.E., B.Ş. Design: W.A., T.O., A.E., B.Ş. Data Collection or Processing: W.A., A.E., Analysis or Interpretation: W.A., A.E., S.A., Literature Search: W.A., Writing: W.A., T.O.,S.A.

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