

## Research Paper: Sexual Dimorphism and Age-Related Variations of Corpus Callosum Using Magnetic Resonance Imaging

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### ABSTRACT

**Introduction:** Despite technological advances and numerous published investigations, sexual dimorphism of Corpus Callosum (CC) remains a matter of ongoing controversy. In the present study on neurologically healthy Iranian adults, we investigated the possible gender- and age-related variations in anthropometric callosal measurements.

**Methods:** Our sample comprised 35 male and 35 female subjects with the mean (SD) age of 42.8 (14.7) and 44.7 (15) years, respectively, who referred to Partow Magnetic Resonance Imaging (MRI) center in North of Iran for headache work-up. Individuals with known neurologic disorders, history of head trauma, left handed subjects, and those younger than 20 and older than 80 years old were excluded. We measured callosal and brain dimensions on the midsagittal section and analyzed the data using Independent sample t test, analysis of variance, analysis of covariance, Pearson correlation coefficient, and linear regression.

**Results:** The unadjusted dimensions were larger in male participants compared to female ones. Corpus callosum area on the midsagittal plane, the longitudinal brain and callosal measurements and dimensions related to the width of CC were significantly larger in males than females ( $P < 0.05$ ). Overall, the longitudinal dimensions of CC were larger in the elderly, while the younger subjects have significantly thicker callosal dimensions. The observed gender-related differences lost their statistical significance after adjusting for longitudinal brain dimensions.

**Conclusion:** We found apparently larger callosal dimensions in the male participants, which could be an artifact caused by the significantly larger male brain dimensions. Our investigations on the less studied racial groups also provide further evidence regarding the confounding effect of brain volume on the observed sexual dimorphism of CC.

### Key Words:

Corpus callosum, Gender, Magnetic Resonance Imaging, Sexual dimorphism

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## 1. Introduction

**C**orpus Callosum (CC) is the principle interhemispheric commissure in brain. As an elongated midline structure, it is composed of 200-800 million horizontal interconnecting homotopical and heterotopical regions.

Similar to the other areas of the brain, mature CC includes neurons and glial cells as well as myelinated and unmyelinated fibers. The human CC has been divided anterior-posteriorly into 5 regions, including the genu, the rostrum, the body or trunk- frequently subdivided into anterior, middle, and posterior body- the isthmus, and the splenium. Whilst the anterior part of the human CC, including genu, rostrum and body contains fibers interconnecting frontal association cortical areas, the isthmus typically includes auditory, somatosensory, and primary motor fibers.

Variations in shape and size of CC and its possible association with cognitive and behavioral implications have always been a topic of interest in the scientific communities. Several lines of studies have highlighted the variations in size and morphology of CC in a wide range of neuropsychiatric disorders [1-5]. Interestingly, some reports have underscored the possible contribution of these morphological variations to the extraordinary levels of mental abilities such as intelligence [6]. Despite rigorous investigations on gender-related variations of CC, much controversy still exists in the literature. It has been concluded that the sexual dimorphism observed in CC anthropometric measurements is real and would remain significant after adjusting for the main proposed confounders, including brain size [7]. On the other hand, a group of studies have attributed the apparent callosal dimorphism between genders to the individual differences in brain size [8, 9].

These inconsistencies could be partly explained by the wide variety of measurement parameters, methods utilized, and subjects studied [10-13]. Moreover, from a statistical point of view, issues like the insufficient power of some studies to detect significant differences, small sample size, and errors of measurement could have contributed to these conflicting reports [14]. Another issue is that most published studies investigated gender- and age-related CC variations in the western countries and few studies addressed it in the Middle Eastern and Asian countries. Yet, not surprisingly, the sexual dimorphism of CC is also a matter of ongoing controversy in the studies in the mentioned racial groups [15-17].

To the best of our knowledge, there is only one published study on the callosal measurements in Iranian sub-

jects; which observed no significant sexual dimorphism in CC morphometrics, but reported variations in CC dimensions compared to the other racial groups [15]. In the present study, we investigated the possible gender- and age-related variations in anthropometric measurements of CC using a magnetic resonance imaging (MRI) database in the North-West of Iran.

## 2. Materials and Methods

Our samples comprised 70 subjects (35 males and 35 females) with mean (SD) age of 43.77 (14.8) years, who referred to Partow MRI center for headache work-up during 2013. Individuals with known neurologic disorders, history of head trauma, left handed subjects and subjects younger than 20 and older than 80 years old were excluded. Also, images of patients with any visible evidence of deviation from the Midsagittal Plane (MSP) were excluded. Finally, the participants were divided into the following age groups; 20-39, 40-59, and 60-80 years.

Brain and CC dimensions of interest were manually traced using Philips DICOM Viewer software (Pms-DView-Informer Technologies, Inc.) in MSP of T1 weighted magnetic resonance image of each subject. The software package enabled us to measure distances along straight lines and areas of the regions of interest using the smoothed polygon option. To minimize the possible measurement error and subjectivity, we asked a radiologist and a radiology technician, who were both blind to the age and sex of the subjects to draw the borders of CC and measure the dimensions and areas of interest on two separate occasions. The interclass and intraclass correlations for inter-rater and intra-rater reliability for different measurements ranged from 0.84 to 0.95 and 0.88 to 0.93, respectively. MSP was determined by using midpoints of the Posterior Commissure (PC), Anterior Commissure (AC), and Interhemispheric Fissure (IF); as previously described by Mitchell et al. [18].

We used following measurements and dimensions for each subject as described previously [15, 19]. Main longitudinal distances were defined as Length Brain (LB): brain length from the occipital to the frontal lobe of the cerebrum; Head Length (HL): head length from the occipital to the frontal lobe of the skull; length of CC (LC); width of CC (WC) in the middle at the center of CC length; maximum rostral width (Wr) of CC below the genu segment; maximum CC width at the splenium (Ws) starting at posterior most point of CC; height of CC (HC): as the distance between a line through the inferior borders of rostrum and splenium and a line parallel to that; maximum (Wmax) and minimum (Wmin)

width of CC in the body; maximum width of the anterior part of body of CC (Wba); excluding genu and rostrum, maximum width of posterior part of body of CC (Wbp), excluding rostrum, distance between anterior most point of CC and anterior commissure (GC); shortest distance from anterior most point of CC to the cortex (AS); shortest distance from topmost point of CC to the cortex (TS); shortest distance from posterior most point of CC to the cortex (PS); distance from frontal lobe of brain to anterior most point of CC (FA); and distance from occipital lobe of brain to posterior most point of CC (OP). Based on the mentioned dimensions, we also calculated the following ratios: LC/LB, WC/LC, WC/LB, W/LC, WC/HC, and checked the possible gender-related variations.

The measured dimensions were tested for age and gender-related differences and measurements were also checked for correlations. SPSS16 (SPSS Inc.) was used for statistical analysis. Independent samples test, analysis of variance, analysis of covariance (ANCOVA), and Pearson correlation coefficient were used to analyze the data. P-values less than 0.05 were considered significant. All subjects gave their written informed consent before taking part in the study. Also, the Institutional Review Board at Shahid Beheshti University of Medical Sciences and Health Services approved the study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki.

### 3. Results

The main longitudinal dimensions were measured as follows; LB:  $16.27 \pm 0.75$  cm (95% CI; 16.09-16.45); and LC:  $7.18 \pm 0.5$  cm (95% CI; 7.06-7.30) with a ratio of 2.6. The main dimensions related to width were measured as follows; WC:  $0.62 \pm 0.12$  cm (95% CI; 0.59-0.65), Wr:  $1.20 \pm 0.2$  cm (95% CI; 1.16-1.25); and Ws:  $1.17 \pm 0.16$  (95% CI; 1.36-1.21). Further details regarding all measured dimensions and ratios are listed in [Table 1](#).

#### Gender-related differences

The unadjusted dimensions were larger in male compared to female participants. Mean of CC area (CCA) was  $6.94 \pm 0.94$  cm<sup>2</sup> in male subjects compared to  $5.94 \pm 0.85$  cm<sup>2</sup> in females with a statistically significant difference ( $P < 0.001$ ). Moreover, the following longitudinal brain and callosal measurements were significantly larger in males rather than females subjects; HL, LB, LC, FA, OP, and GC. This trend was also observed in the dimensions related to the width of CC and the shortest distance to the cortex, including Wr, Ws, WC, Wmax, Wba, AS, TS, and PS. Further details and P-values are listed in [Table 2](#).

#### Age-related differences

Overall, the longitudinal dimensions of CC were larger in the elderly, while in the young participants the dimensions related to the width of CC were significantly larger. HC, LC, and LC/LB were significantly larger in the 60–80 years age group, compared to the other age groups. WC, Wr, AS, FA, and WC/LC were significantly larger in the 20–40 years age group, compared to the 60–80 years age group. Moreover, our data revealed that in studied samples, TS was larger in the 40–60 years age group in comparison with the other two age groups.

#### Adjustment for age and brain length

The gender-related difference in HL and GC remained significant after adjusting for age. Furthermore, after adjusting the raw comparisons for proxies of brain length, including LB, the observed gender-related differences in callosal measurements lost their statistical significance.

#### Correlation

Age and LC and age and LC/LB were positively correlated ( $r = +0.323$ ,  $P = 0.006$  and  $r = +0.259$ ,  $P = 0.030$ , respectively) while negative correlation was observed between age and Wmax ( $r = -0.297$ ,  $P = 0.012$ ) and age and AS ( $r = -0.292$ ,  $P = 0.014$ ).

### 4. Discussion

Despite technological advances and numerous published investigations on the topic, sexual dimorphism of CC remains a matter of ongoing controversy. Some studies attributed the observed gender related differences to confounding factors, including brain volume [8, 20, 21] or allometric variations [22]. However, some investigators have reported a significant gender difference in shape and morphology of the human CC, which survived adjustment for the proposed confounding factors [7, 23]. In the present study conducted on healthy Iranian subjects, we found larger brain and callosal dimensions in the male participants compared to female ones, which lost their statistical significance after adjusting for longitudinal brain dimensions.

In contrast to our findings, there are reports in the literature that highlighted gender-related differences in callosal measurements even after adjusting for brain volume by different methodologies. Using covariate, regression and ratio analysis and also a subset of men and women with matched intracranial volume, Sullivan and colleagues observed larger size of CC in male subjects and

Table 1. The main longitudinal dimensions.

(Confidence Interval 95%)			
	Mean	Lower	Upper
CCA (mm <sup>2</sup> )	644.46257	620.0047	668.9204
HL	187.11657	185.3943	188.8389
LB	162.78357	160.9937	164.5734
LC	71.82443	70.6138	73.0351
WC	6.21029	5.9111	6.5095
Wmax	7.13114	6.8579	7.4043
Wmin	4.30443	4.0234	4.5855
Wba	6.98900	6.7087	7.2693
Wbp	6.44129	6.1493	6.7333
Wr	12.08943	11.6015	12.5773
Ws	11.76986	11.3656	12.1741
HC	25.47857	24.7683	26.1889
GC	28.54986	28.0524	29.0473
AS	34.77786	34.0651	35.4906
TS	37.49186	36.8498	38.1339
PS	45.91929	45.0883	46.7502
AF	37.29271	36.5288	38.0567
OP	58.57029	57.4823	59.6582
LC/LB	0.44129	0.4353	0.4472
Ws/LC	0.16405	0.1588	0.1693
Ws/LB	0.07238	0.0699	0.0749
WC/LC	0.08665	0.0825	0.0908
WC/HC	0.24556	0.2335	0.2576

Data is presented in mm.

ANATOMICAL SCIENCES

Abbreviations: CCA: Corpus Callosum Area; HL: Head Length from the occipital to the frontal lobe of cerebrum; LB: Brain Length from the occipital to the frontal lobe of cerebrum; LC: Length of CC; WC: Width of CC; Wmax: Maximum Width of body segment of CC; Wmin: Minimum Width of body segment of CC; Wba: Maximum Width at Anterior Body of CC minus genu and rostrum; Wbp: Maximum Width at Posterior Body of CC minus rostrum; Wr: Maximum Rostral width of CC below the genu; Ws: Maximum CC Width at the Splenium starting at posterior most point of CC; HC: Height of CC; GC: Distance from anterior most point of CC to anterior commissure; AS: Shortest distance from Anterior most point of CC to the cortex; TS: Shortest distance from Topmost point of CC to the cortex; PS: Shortest distance from Posterior most point of CC to the cortex; FA: Distance from Frontal lobe of brain to Anterior most point of CC; OP: Distance from Occipital lobe to the Posterior most point of CC.

○ **Table 2.** The unadjusted dimensions of CC in male and female participants.

	Male Mean (SD)	Female Mean (SD)
CCA (mm <sup>2</sup> )**	694.47(94.45)	594.45(85.32)
HL**	190.23(6.59)	184.00(6.51)
LB**	166.39(6.32)	159.18(6.89)
LC**	73.78(4.65)	69.87(4.77)
WC*	6.51(1.26)	5.91(1.19)
Wmax*	7.41(0.97)	6.85(1.24)
Wmin	4.52(1.27)	4.09(1.05)
Wba*	7.27(1.05)	6.71(1.24)
Wbp	6.68(1.24)	6.21(1.17)
Wr*	12.73(1.98)	11.45(1.93)
Ws*	12.32(1.49)	11.22(1.72)
HC	26.08(2.81)	24.88(3.05)
GC*	29.23(1.89)	27.87(2.07)
AS*	35.53(3.04)	34.03(2.77)
TS*	38.28(2.26)	36.70(2.88)
PS*	47.17(3.47)	44.67(3.06)
FA*	38.31(2.96)	36.27(3.14)
OP*	59.92(4.52)	57.22(4.24)
LC/LB	0.443(0.024)	0.439(0.025)
Ws/LC	0.167(0.020)	0.160(0.023)
Ws/LB	0.074(0.009)	0.070(0.113)
WC/LC	0.088(0.165)	0.085(0.182)
WC/HC	0.251(0.519)	0.239(0.491)

Data is presented in mm. \* P<0.05. \*\* P<0.001.

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Abbreviations: CCA: Corpus Callosum Area; HL: Head Length from the occipital to the frontal lobe of cerebrum; LB: Brain Length from the occipital to the frontal lobe of cerebrum; LC: length of CC; WC: width of CC; Wmax: Maximum Width of body segment of CC; Wmin: Minimum Width of body segment of CC; Wba: Maximum Width at Anterior Body of CC minus genu and rostrum; Wbp: Maximum Width at Posterior Body of CC minus rostrum; Wr: Maximum Rostral width of CC below the genu; Ws: Maximum CC width at the Splenium starting at posterior most point of CC; HC: Height of CC; GC: Distance from anterior most point to CC and anterior commissure; AS: Shortest distance from Anterior most point of CC to the cortex; TS: Shortest distance from Topmost point of CC to the cortex; PS: Shortest distance from Posterior most point of CC to the cortex; FA: Distance from Frontal lobe of brain to Anterior most point of CC; OP: Distance from Occipital lobe to the Posterior most point of CC.

concluded that this observation could not be a simple artifact and might have biologic significance regarding the connectivity differences in male and female brains [23]. Also, in contrast to our findings, a more recent

study published by Ardakani et al. reported larger CCA in females after statistical adjustment for brain size using a large sample from the OSIS (Open Access Series of Imaging Studies) database [7].

Our results are in line with the findings of Luders et al. who reported thicker CC in male subjects that hardly remained when brain-size matched subjects were analyzed. They showed that brain size had a significant impact on the observed sexual dimorphism in CC measurements [8]. In another study, Leonard and associates used hierarchical multiple regression methods and ANCOVA to investigate the previous reports on sexual dimorphism of brain structures and found that most variations were caused by differences in cerebral volume [24]. Their analyses revealed that the observed larger relative size of CC in female subjects can be fully explained by the associated relative callosal and brain dimensions. A meta-analysis on the previous studies also confirmed the disappearance of detected gender-related differences upon adjusting for brain size [20]. Moreover, our results are in agreement with the previously published study on Iranian subjects which did not detect a significant gender-related difference in callosal dimensions [15].

Various explanations have been offered by experts regarding the inhomogeneity of the published studies. An important issue addressed by Bermudez et al. is that using different normalization strategies and analytical approaches could result in different conclusions and these methods are not necessarily interchangeable [11]. Use of ratios or analysis of covariance as different statistical methods has been considered as a source of these conflicting reports [13, 20]. Moreover, the considerable individual variations in CC morphology, the insufficient power of some studies and low sample size could be regarded as a possible limitation for some of the studies that failed to detect a statistically significant difference between genders [7, 25].

Use of different and error prone estimates of brain volume by some authors is also a contributing factor to the conflicting reports on sexual dimorphism of CC [13, 14]. Previous studies have also highlighted the noticeable callosal measurement errors that could result from variations in the selection of MSP [26]. Another source of error is the manual tracing of CC borders [27] and the possibility of inter-rater and intra-rater variability. Finally, the probable racial differences in CC anatomy might have played a role in this controversy.

Most studies on sexual dimorphism of callosal morphology have been conducted in the western countries on the Caucasian population and the few studies in other racial groups have reported significant differences in anthropometric measurements of CC [28]. One study has documented the variations of CC parameters and morphology among the Indian, Caucasian, and Japanese

population [15]. Our observed CC dimensions are larger than Thai [29], Greek [30], and Japanese [16], but similar to Indian population [19, 31].

Regarding the observed changes in CC dimensions, our findings on the increase of LC and decrease in WC with age were comparable with the results of many studies on this topic [16, 19, 31, 32], but was in contrast with the study on Iranian subjects in which they reported an increase in CC dimensions in the 40–60 age group [15].

This study has some limitations that deserve comment. First of all, we did not use automatic methods for MSP detection that could introduce error in our observations. Moreover the manual delineation of the dimensions of interest could be a probable source of variability. To minimize the effect of these issues we asked two experts; a radiologist and a physician to select the MSP and trace the desired dimensions manually twice and the observed inter- and intra-rater variability showed acceptable reproducibility of our observations. Another issue that must be addressed is the limitation we had to reliably estimate brain volume of the subjects and due to imprecise estimates available in our center we decided to use brain length as a proxy to adjust for the longitudinal CC dimensions. Also, our study might not be statistically powered enough to detect some possible differences between genders.

To recapitulate, in the current study, we presented further evidence that the apparent sexual dimorphism in callosal measurements could be due to the confounding effect of brain volume differences between genders. This study also suggests that despite the observed racial variations in CC morphology, the role of brain volume as a confounding factor could be generalized to different racial groups. Furthermore, we observed increase in the longitudinal callosal dimensions and decrease in width of CC in the older age groups.

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### Conflict of Interest

All authors certify that this manuscript has neither been published in whole nor in part nor being considered for publication elsewhere. The authors have no conflicts of interest to declare.

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