

# Corpus callosum morphology of healthy children: a structural magnetic resonance imaging study from Turkey

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## SUMMARY

Morphological measurement of corpus callosum (CC) in magnetic resonance imaging studies has an important value for clinical decision-making during the period of childhood. Although there is evidence for differences in brain morphology in terms of socioeconomic disparities, there is no research specifically on CC morphology from any low- and middle-income countries. This study aims to report structural measurements and area of CC of healthy children from Turkey, a middle-income country, and find out whether the CC morphology differs between male and female children in different age groups. Healthy children aged 6-18 years were recruited retrospectively and their CC antero-posterior (AP) length, genu, body and splenium width (GW, BW, SW) and CC midsagittal area were measured from magnetic resonance imaging studies. Independent sample t-test was used to compare CC measurements of the sex and age groups. Pearson correlation test was used to determine linear correlations between age and CC parameters. The sample consisted of 200 healthy children; at least 5 female and 5 male children for each age; 103 (51.5%) females, 97 (45.5%) males.

There was a positive correlation between the age and CC AP length ( $r=0.248$ ,  $p<0.001$ ) and SW ( $r=0.325$ ,  $p<0.001$ ) as well as midsagittal area ( $r=0.191$ ,  $p<0.007$ ). The CC AP length, GW, BW, SW and area were not different statistically between sex groups.

This study is the first report providing age and sex-related morphological measurements of CC of healthy children in Turkey. The findings may be helpful for clinicians and researchers from Turkey as well as other low- and middle-income countries.

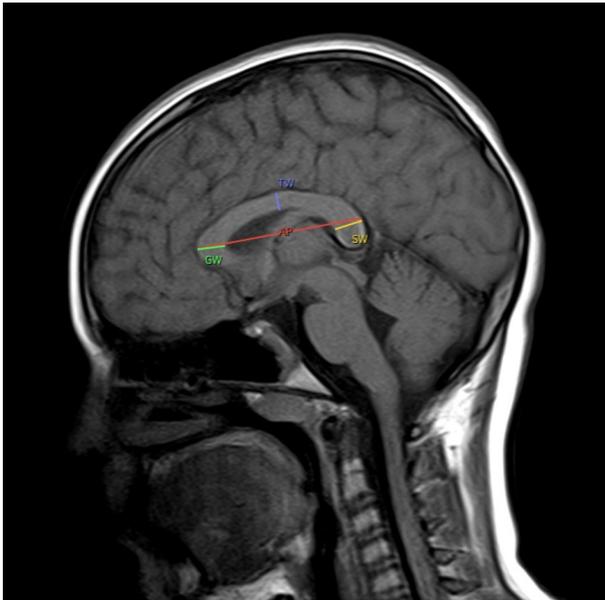
**Key words:** Corpus callosum – Magnetic resonance imaging – Morphological and microscopic findings – Child – Age factors

## INTRODUCTION

The corpus callosum (CC) is the largest white matter commissure and it consists of rostrum, genu, body, and splenium, connecting and coordinating the cerebral hemispheres functionally and structurally (Aboitiz et al., 1992). There are variations in the morphology of CC during childhood related to axonal growth, pruning and myelination. Evaluating the width of different parts of CC on Magnetic Resonance Imaging (MRI) is important for clinical decision-making in the childhood period, particularly the abnormal thinning and thickening of CC (Andronikou et al., 2015). The corpus callosum morphology has been studied in

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**Fig 1.** Midsagittal T1A MR image demonstrating corpus callosum measurements of anteroposterior length, genu, truncus and splenium widths.

healthy children by many researchers from high income countries (HICs) (Giedd et al., 1999; Luders et al., 2010; Westerhausen et al., 2016; Keshavan et al., 2002; Garel et al., 2011; Chavarria et al., 2014; Tanaka-Arakawa et al., 2015). The literature includes contradictory evidence on sex-related differences in CC development in childhood and puberty (Keshavan et al., 2002; Giedd et al., 1997; DeBellis et al., 2001; Paus et al., 2010). Although there is evidence for differences in brain morphology in case of socioeconomic differences (Piccolo et al., 2016; Jenkins et al., 2020), we did not identify any research specifically on CC morphology from any low- and middle-income countries (LMICs).

Our aim was to review the literature and to report morphological measurements and area of CC of healthy children from Turkey, a middle-income country. Secondly we aimed to find out whether the CC area and measurements differ between male and female children during childhood and puberty.

## MATERIALS AND METHODS

**Study design and participants.** In a retrospective design, children aged 6-18 years who had a completely normal cranial MRI at Ankara Yıldırım Bayazit University, Yenimahalle Training and Research Hospital Radiology Department (AYRD) who had pediatric neurology examination reports were recruited for the study between October 1, 2015 and October 1, 2019. A pediatric neurologist screened health records of children whose parents provided written consent for the study. The children were not included in the sample if they had any of the following conditions: a history of prena-

tal drug use, perinatal problems, preterm birth, epilepsy, brain mass, vascular malformations, neurometabolic diseases, cerebral palsy, intellectual disability, learning disability, developmental delay, autism spectrum disorder, attention deficit hyperactivity disorder, and genetic disorder, as well as an abnormal neurological examination. For each age between 6 to 18, at least 5 healthy boys and 5 healthy girls were planned to be involved in the sample.

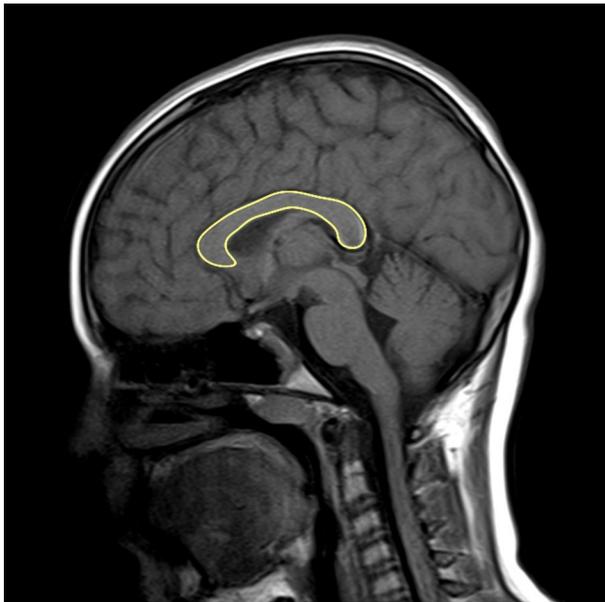
To define age groups between 6 to 18 years, we used merged age groups with 3 years interval similar to the previous CC measurement literatures (Luders et al., 2010; Tanaka-Arakawa et al., 2015). Although pubertal age can change individually according to hormonal levels, sex and genetic factors (Khan, 2019), children aged from 6 years to 11 years and 11 months were considered as childhood age group, and from 12 years to 17 years and 11 months were considered as pubertal age group in our study.

The study was approved by the Ethics Committee of the Ankara Yıldırım Bayazit University, Yenimahalle Training and Research Hospital.

Corpus callosum dimensions of the children were measured on sagittal T1-weighted spin echo images (TR 800 ms, TE 15 ms, 230 mm × 230 mm FOV, 5 mm slice thickness, 1mm interslice gap) with Siemens Magnetom Avanto 1.5 T MRI Unit. Length between anterior-most and posterior-most points of CC was defined as anterior-posterior (AP) length. According to the maximum straight length by Witelson's method (Mourgela et al., 2007) CC is divided into 3 parts: 1) anterior third was defined as genu, and the width between inner and outer anterior-most points was recorded as genu width. (GW), 2) The mid-third of the CC was defined as body, and width of the widest part of body was recorded as body width (BW), 3) The posterior third was defined as splenium, and width of the widest part of splenium was recorded as splenium width (SW) (Fig. 1). The corpus callosum area was measured by defining the CC borders manually with a software (Osirix MD; Pixmeo SARL, Switzerland) on the mid sagittal images (Fig. 2). An experienced radiologist (the first author) measured all parameters.

## Data analyses

Descriptive statistics were given as means and standard deviations (SD) for normal distributions; minimum and maximum values were given for age and sex groups. Independent sample t-test was used to compare CC measurements of sexes and age groups. Pearson correlation test was used to determine linear correlation between quantitative variables. For statistical significance  $p < 0.05$  was used. Statistical analyses were done using IBM SPSS 20.0 (SPSS Inc., Chicago, IL, USA) package program.



**Fig 2.** Midsagittal T1A MR image demonstrating corpus callosum area measurement.

BW was  $5.69 \pm 0.91$  mm, SW was  $8.91 \pm 1.37$  mm and the CC area was  $5.70 \pm 0.92$  cm<sup>2</sup>. Morphological measurements of CC AP length, genu, body, splenium widths and midsagittal area according to sex and age groups are given in Table 2. To examine possible pubertal sex differences in CC measurements, sex differences are analyzed in two age groups: 6 years to 11 years and 11 months, 12 years to 17 years and 11 months. No differences were found in CC AP length, GW, BW, SW and area in terms of sex as seen in Table 3. The CC SW and area were significantly higher in pubertal age group ( $p=0.001$  for SW,  $p=0.013$  for CC area), but CC AP length, BW and GW were not statistically different between groups ( $p=0.060$  for AP length,  $p=0.360$  for BW,  $p=0.611$ ).

There was a positive correlation between the age and CC AP length ( $r=0.248$ ,  $p<0.001$ ) and SW ( $r=0.325$ ,  $p<0.001$ ) as well as midsagittal area ( $r=0.191$ ,  $p<0.007$ ) as seen in Fig. 3, but there was no significant correlation for CC GW ( $r=0.055$ ,  $p=0.436$ ) and BW ( $r=0.111$ ,  $p=0.118$ ) and age.

**RESULTS**

The sample consisted of 200 healthy children. Of the total, 103 children were female (51.5%) and 97 were male (48.5%). Distribution of the children based on sex and age are given in Table 1. The mean age was  $12.03 \pm 3.16$  SD. The mean age of the female children was  $12.23 \pm 3.10$ ; male children was  $11.91 \pm 3.23$  and the difference was not different statistically between sexes ( $p=0.482$ ).

In the total sample, the mean value for CC AP length was  $66.1 \pm 4.8$  mm, GW was  $7.19 \pm 1.11$  mm,

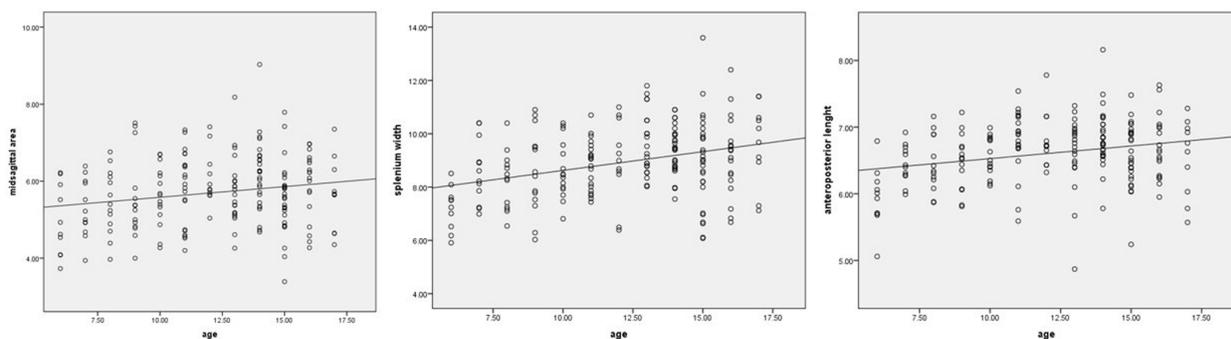
**DISCUSSION**

This study is the first report of the morphological measurements of corpus callosum substructures and midsagittal area in MRI of healthy children from Turkey. As the morphology of CC during childhood is important for clinicians and researchers, our study adds new information to the literature by reporting age and sex-related measurements of CC from a middle-income country.

The AP length, SW and area of CC in MRI were correlated to age between 6 and 18 years. These results are consistent with other structural MRI

**Table 1.** Frequency of the children in the sample based on sex and age

	Age in years (n)											
Sex (n)	6	7	8	9	10	11	12	13	14	15	16	17
Male (n)	5	7	8	7	5	11	6	8	14	14	7	5
Female (n)	5	5	5	7	10	10	5	13	13	14	11	5
Total n (%)	10	12	13	14	15	21	11	21	27	28	18	10
N=200	(5.0)	(6.0)	(6.5)	(7.0)	(7.5)	(10.5)	(5.5)	(10.5)	(13.5)	(14.0)	(9.0)	(5.0)



**Fig 3.** Correlation between the age and corpus callosum anteroposterior length, splenium width and midsagittal area ( $r=0.248$ ,  $p<0.001$ ;  $r=0.325$ ,  $p<0.001$  and  $r=0.191$ ,  $p<0.007$  respectively).

**Table 2.** Morphological measurements of CC AP length, genu, body, splenium widths and midsagittal area according to sex and age groups

<b>GIRLS</b>	<b>6-8 years</b>	<b>9-11 years</b>	<b>12-14 years</b>	<b>15-17 years</b>
<b>AP length (mm)</b>				
Mean±SD	62.6±4.0	65.2±4.0	68.1±3.8	65.5±3.5
Min	57.0	55.9	57.8	57.8
Max	69.9	71.8	77.8	72.2
<b>GW (mm)</b>				
Mean±SD	7.18±0.83	7.08±1.04	6.93±1.08	7.14±1.22
Min	5.90	5.51	4.88	4.65
Max	8.50	9.90	9.76	10.70
<b>BW (mm)</b>				
Mean±SD	5.52±1.12	5.61±0.86	5.72±0.58	5.61±0.80
Min	4.37	3.97	4.63	3.88
Max	8.70	7.57	6.87	7.63
<b>SW (mm)</b>				
Mean±SD	7.80±1.02	8.36±1.19	9.22±1.10	9.20±1.46
Min	6.18	6.03	6.39	6.68
Max	10.40	10.7	11.3	12.40
<b>CC area (cm<sup>2</sup>)</b>				
Mean±SD	5.37±0.82	5.41±0.82	5.78±0.78	5.62±0.77
Min	3.73	4.00	4.26	4.27
Max	6.53	7.26	7.41	7.35
<b>BOYS</b>	<b>6-8 years</b>	<b>9-11 years</b>	<b>12-14 years</b>	<b>15-17 years</b>
<b>AP length (mm)</b>				
Mean±SD	62.4±4.8	67.6±4.4	66.9±5.8	66.9±6.0
Min	50.6	57.6	48.7	52.4
Max	71.6	75.4	81.6	76.3
<b>GW (mm)</b>				
Mean±SD	6.87±1.17	7.45±1.22	7.61±1.17	7.27±0.92
Min	5.39	6.07	6.03	4.87
Max	9.36	11.50	10.40	8.51
<b>BW (mm)</b>				
Mean±SD	5.53±0.51	5.60±0.83	6.14±1.04	5.76±0.83
Min	4.62	4.07	4.57	4.20
Max	6.26	6.98	8.54	7.35
<b>SW (mm)</b>				
Mean±SD	8.25±1.26	9.11±0.99	9.60±1.16	9.08±1.78
Min	5.91	7.44	7.55	6.08
Max	10.40	10.90	11.80	13.60
<b>CC area (cm<sup>2</sup>)</b>				
Mean±SD	5.18±0.85	6.00±0.98	6.22±0.94	5.73±1.05
Min	3.94	4.27	4.61	3.39
Max	6.76	7.51	9.03	7.79

studies from high income countries such as United States (US), France, Australia (Giedd et al., 1999; Luders et al., 2010; Westerhausen et al., 2016; Keshavan et al., 2002; Giedd et al., 1997; DeBellis et al., 2001; Garel et al., 2011; Tanaka-Arakawa et al., 2015). Our findings are also supported by behavioral research showing changes in functional interhemispheric interaction and development in similar age groups (Banich and Brown, 2000; Westerhausen et al., 2010). In the pubertal age group, CC SW and midsagittal area were significantly higher than childhood age group. This finding is also consistent with the studies from US (Giedd et al., 1999; Luders et al., 2010; Chavarria et al., 2014).

Four studies that aimed to report healthy children's CC morphology in MRI examinations as a function of age from HICs are summarized and

compared to our study in Table 4. Giedd et al. (1996) provided CC area measurements, and, similar to our study, they found that CC area increased with age. Secondly, Garel et al. (2011) reported median CC measurements in MR examinations in 622 healthy children. For example, the authors reported that for age 7, median AP length was 66mm, 3rd percentile was 57.4mm, 97th percentile was 75.4mm, whereas in our study mean AP length between the ages of 6-8 was 62.6 mm in girls (min: 57.0 mm, max: 69.9 mm), and 62.4 mm in boys (min: 50.6 mm, max: 71.6 mm). However, their reported SWs were 10 to 15 mm higher than our results (Garel et al., 2011). As both studies excluded ischemic diseases, neurologic and metabolic disorders that are known to effect CC splenium morphology (Park et al., 2017), it may be speculated that there may be functional and ana-

**Table 3.** Measurements of corpus callosum according to childhood and puberty age groups

6 years-11 years 11 months age group N=85			
	Boys (n=43)	Girls (n=42)	P
	Mean±SD	Mean±SD	
AP	65.6±5.0	64.2±4.1	0.186
Genu	7.18±1.22	7.11±0.96	0.773
Body	5.57±0.69	5.48±1.23	0.682
Splenium	8.71±1.19	8.16±1.15	0.033
Area	5.62±1.00	5.40±0.81	0.264
12 years- 17 years 11 months age group N=115			
	Boys (n=54)	Girls (n=61)	P
	Mean±SD	Mean±SD	
AP	67.0±5.9	66.8±3.8	0.835
Genu	7.45±1.06	7.03±1.15	0.053
Body	5.98±0.96	5.66±0.69	0.065
Splenium	9.38±1.50	9.21±1.28	0.584
Area	6.01±1.03	5.70±0.77	0.094
Overall sample N=200			
	Boys (n=54)	Girls (n=61)	P
	Mean±SD	Mean±SD	
AP	66.3±5.5	65.8±4.1	0.441
Genu	7.33±1.13	7.07±1.07	0.092
Body	5.78±0.87	5.59±0.95	0.127
Splenium	9.06±1.40	8.78±1.32	0.139
Area	5.82±1.02	5.58±1.02	0.061

tomical reasons behind different splenium measurements that were not controlled in studies. Environmental and socioeconomic factors may differ between countries (Jenkins et al., 2020), which may affect the differences of the results. Lastly, differences may be due to interobserver differences in measurements. A third study on CC mor-

phology reported CC and its substructures' areas from Japan (Tanaka-Arakawa et al., 2015), in which 54 children between 10 to 18 years of age are included. The area measurements were similar between studies. Lastly, in Vannucci et al's report age groups and GW, SW and AP length measurements of CC were similar between studies

**Table 4.** Summary of studies on healthy children's corpus callosum morphology in magnetic resonance imaging study examinations

Study	Design	Country	Sample size	Age groups	Measurements
Giedd et al., 1996	Cross sectional	US	114	4-18 years	Mean CC area
Giedd et al., 1999	Longitudinal	US	139	5-18 years	Mean rostrum, genu, rostral body, anterior midbody, posterior midbody, isthmus, splenium
Garel et al., 2011	Cross sectional	France	622	1 day-15 years	Median, 3 <sup>rd</sup> percentile and 97 <sup>th</sup> percentile of anteroposterior diameter, CC length, genu, body, isthmus, splenium, frontooccipital diameter, splenium-tegmentum distance for age
Tanaka-Arakawa et al., 2015	Cross sectional	Japan	114	1 month- 25 years	Areas of rostrum, genu, rostral body, anterior midbody, posterior midbody, isthmus, splenium, total CC
Vannucci et al., 2017	Cross sectional	US	118	1 week- 18.7 years	Genu length, genu height, splenial length, splenial height, total length, CC area

(Vannucci et al., 2017).

In terms of sexual differences in CC development during the childhood period, two reports from US reported no sexual dimorphism (Giedd et al., 1997; Rajapakse et al., 1996). Similarly, our findings convey that there is no sex difference in terms of measured absolute CC structures. A number of studies from US reported that there is significant difference of the midsagittal area values of CC between male and female patients during childhood in favor of males, contradicting our study (Luders et al., 2010; DeBellis et al., 2001; Lenroot et al., 2007).

It seems that the general trend of increase in CC SW and midsagittal area with age during childhood period is similar between studies from HICs and our study. However, the exact measurements differ across countries. The different results may be related to heterogeneity of age periods, developmental status of children and techniques of measurements. Further studies on CC morphology are needed from LMICs to examine if differences exist across countries.

Alternations in the morphology of CC may indicate many pathologies like white matter diseases, congenital and vascular anomalies, premature birth, autism spectrum disorder, attention deficit hyperactivity disorder (Gilliam et al., 2011; Hyun Yoo et al., 2012; Krupa et al., 2013; Sripada et al., 2018; Levman et al., 2018). It is a strength that all these conditions are excluded by a pediatric neurologist and that all images were interpreted as normal by an experienced radiologist. Evaluating CC morphology in MRI studies helps clinical decision-making, while thinning and thickening of CC is reported mostly based on subjective judgments (Shupper et al., 2016). Our study reported objective CC morphological measurements from Turkey. As recent literature claimed that socioeconomic differences may effect CC structures (Duffons et al., 2020), our results inform clinicians and researchers on objective measurements of CC of the healthy children in different age groups from a middle income country.

This study has many limitations. Our study is limited in generalization, because our sample is from the capital of Turkey and healthy but for some reason, they have been a subject for cranial MRI indication like headaches. The measurements were done manually and by only one radiologist. The brain volume and ratio of CC measurements to brain volume were not provided in this study. Retrospective screening of the health records may lead to transfer bias due to loss of information. In spite of these limitations, this is the first study that collected a broad range of absolute CC measurements of healthy children from a middle-income country, Turkey, and reported several similarities and differences in terms of CC morphology between other studies from HICs.

The results of this study provided age- and sex-

related measurements of CC of healthy children in Turkey. The findings may be helpful for clinicians and researchers from Turkey as well as other LMICs.

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