Age and sex related variations in Corpus Callosal morphology

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ABSTRACT

There is no unanimity in literature on sexual dimorphism or on age related morphophometric changes in the Corpus Callosum (CC). For comprehensive data 44 preserved human brains (22 male and 22 female) and 30 MRI scans from North-west Indian population were studied. Morphometric measurements of the CC and its subregions were taken at the midsagittal level in both the groups and subjected to statistical analysis. The only CC parameters which showed sexual dimorphism were (a) larger CC length in males in the MRI group, (b) the distance between the splenium and superior colliculus was more in males in preserved brains and (c) The distance between the genu and the fornix was more in older males than older females. Age related changes included (a) In males the distance between the genu and the fornix (in both the groups) was more in the older age group while the maximum width of the anterior half of the CC body was more in the younger age group (preserved brains) and (b) In females the height of the CC and the minimum width of the CC were more in the older females (preserved brains). No sexual dimorphism was observed in most of the CC parameters studied, including the splenium. Age related thinning of the anterior half of the CC in males could possibly be related to atrophic brain changes more common in males than females.

Key words: Aging, autopsy; corpus callosum, MRI scan, sex dimorphism, India.

INTRODUCTION

Corpus callosum (CC) is the main fiber tract connecting the cortical and subcortical regions of the right and left hemispheres and plays an essential role in the integration of information between the two hemispheres.

There is no unanimity in literature on the subject of sexual dimorphism of the human corpus callosum. Several studies have found significant sex differences in the length, shape and area of the corpus callosum of males and females; with females having larger relative splenial width.[1-5] Sexual dimorphism in CC might be due to greater bihemispherical representation of cognitive functions in females. This might not simply be due to sex related differences in brain size and may reflect difference in connectivity necessitated by differences in brain size.[6] On the other hand, there are many reports where no sex related differences in the size and various other measurements of corpus callosum have been reported.[7-9] Conclusions regarding age related changes in the corpus callosum have also not been consistent in various studies available. Age changes in specific regions of corpus callosum have been documented and may indicate alteration of the inter-hemispheric fiber systems.

Most of the studies of CC measurements have been performed on Caucasian samples [6,7,9-15] and there are very few studies of CC in the Indian population.[16,17] Moreover greater numbers of studies are carried out on MRI scans. MRI and cadaver based studies are radically different approaches each with its own advantages and disadvantages. The present study was conducted using both formalin fixed preserved brains and MRI scans to get comprehensive data regarding gender and age related differences of CC in normal adult population in northwest region of India.

METHODS

This study was carried out in Department of Anatomy, Government Medical College and Hospital, Chandigarh, India over the period of two years from October 2003 to September 2005. The study material consisted of two groups (a) preserved (formalin fixed) brain specimens and (b) MRI brain scans. In both the sets adult human brains/MRI scans (age range 20-60 years) of both males and females were studied. The brain specimens as well as MRI scans were of people with no intracranial mass lesions, head injury or recorded brain pathology. The same measurements were taken in both the sets.

The following techniques were used for each group:

(a) Preserved brain specimens: Forty-four (22 males and 22 females) normal adult brains were obtained from cadavers preserved routinely for use in dissection hall. The mean age of this group was 36.7 years (range 20-60 years). The gender, age and available medical history

Table-1: Gender related differences in preserved brains

Parameter	Male	Female	p value
S'-SC (all ages)	0.86+/-0.18	0.67+/-0.20	0.00185
G-F (40-60yrs)	2.70+/-0.41	2.27+/-0.26	0.00808

All measurements are in centimeters.

- S'-Sc Length: Distance between anterior edge of splenium to superior most point of superior colliculus.
- G-F Length: Distance between anterior edge of genu to anterior edge of columns of fornix.

were noted from the records. Sagittal section of brain was done from front to back with the cut passing through septum pellucidum (Fig. 1). Various callosal distances and dimensions, as mentioned below, were measured with a vernier caliper. All measurements were made twice and the mean value for each parameter was calculated.

(b) MRI scans of the brain: In this group, MRI scans of 30 adults (19 males and 11 females) were included. The mean age of the cases in this group was 36.2 years (range 20-60 years). The scans were taken on 1.5 tesla Siemens Vision machine. The scan film showing mid sagittal section of brain passing through the CC was chosen for measurement (Fig. 2). The corpora were realigned to show the maximum length before choosing the anterior and posterior most points. The measurements were taken directly from MRI films with a vernier caliper. The values were normalized for the full size according to the scale for each scan as follows: in each scan, measurements were first taken from the scans with a vernier caliper. The magnification factor was calculated from the scale given on each film where each division corresponds to one cm. The value obtained by measuring the parameter by vernier caliper was then multiplied by the magnification factor.

The following sets of measurements were taken. (Fig. 3 and 4):

1. Length of corpus callosum (Lc): from anterior most point of CC to its posterior most point.
2. Width of body of corpus callosum at mid point (W).Width of CC was measured at the midpoint, which was taken at the center of the CC length.
3. Maximum width of rostrum (Wr): taken just below the genu.
4. Maximum width of splenium (Ws): taken as shown in fig.4, with starting point at posterior most point of CC.
5. Height of corpus callosum (Hc): A line was taken through inferior border of rostrum and splenium. Another line parallel to this was taken through the top most point of CC. Distance between these two lines was recorded as height of CC.
6. Maximum and minimum width of body of CC (Wmax and Wmi).
7. Maximum width of anterior half of CC body (By the line at the mid point CC was divided into anterior and posterior halves. This measurement was taken at the point of maximum width in the anterior half but genu and rostrum were excluded.) (WBA).
8. Maximum width of posterior half of CC body (Maximum width was measured in the posterior half of CC excluding splenium) (WBP).
9. G-F Length: Distance between anterior edges of

Fig 1: Midsagittal section through corpus callosum in a preserved brain Specimen.

Fig 2: Midsagittal MRI scan

Table-2: Gender related differences in MRI scans

Parameter	Male	Female	p value
LB (all ages)	16.44+/-1.06	15.20+/-0.82	0.00233
Lc (all ages)	7.57+/-0.62	7.10+/-0.41	0.03372
G-F (all ages)	3.01+/-0.30	2.73+/-0.28	0.02037
A-S (all ages)	3.58+/-0.36	3.27+/-0.39	0.03424
P-S (all ages)	4.67+/-0.57	4.02+/-0.34	0.00179
F-A (all ages)	3.69+/-0.53	3.23+/-0.29	0.01194
O-P (all ages)	5.86+/-0.81	4.96+/-0.47	0.00221
Ws (40-60yrs)	1.18+/-0.14	1.43+/-0.13	0.02737

All measurements are in centimeters.

- LB: Length of brain from frontal pole to occipital pole in midsagittal section.
- Lc: Length of corpus callosum from anterior most point of CC to its posterior most point.
- G-F Length: Distance between anterior edge of genu to anterior edge of columns of fornix.
- A-S: Shortest distance from anterior most point of CC to cortical surface.
- P-S: Shortest distance from posterior most point of CC to cortical surface.
- F-A: Distance from frontal pole of brain to anterior most point of CC.
- O-P: Distance from occipital pole of brain to posterior most point of CC.
- Ws: Maximum width of splenium

genu (same as the anterior most point of CC) to anterior edge of columns of fornix.

10. G-C Length: Distance between anterior edge of genu (same as the anterior most point of CC) to anterior edge of anterior commissure.
11. S'-Sc Length: Distance between anterior edge of splenium to superior most point of superior colliculus.
12. Shortest distance from anterior most point of CC to cortical surface (A-S).
13. Shortest distance from top most point of CC to cortical surface (T-S).
14. Shortest distance from posterior most point of CC to cortical surface (P-S)
15. Length of brain (LB): From frontal pole to occipital pole of brain in midsagittal section.
16. Distance from frontal pole of brain to anterior most point of CC (F-A).
17. Distance from occipital pole of brain to posterior most point of CC (O-P)

Ratios

18. Length of CC / length of brain (Lc/LB).
19. Splenial width / length of CC (Ws/Lc).
20. Splenial width / length of brain (Ws/LB).
21. Width of body at mid point / length of CC (W/Lc).
22. Width of body at mid point / height of CC (W/Hc).

RESULTS

The values of the various CC parameters were measured individually in each specimen. Statistical analysis of the different CC parameters was done to compare sexual dimorphism and age related changes using unpaired student 't' test and 'ANOVA' test.

Gender related differences

(a) Preserved brain specimens: The comparison of the mean values of various CC parameters between the two sexes and the corresponding p values are tabulated in Table 1. Statistically significant differences were observed in the following parameters.

1. The distance S'-Sc (splenium-superior colliculus) was 0.86 cm in males and 0.67 cm in females. S'-Sc was thus significantly greater in males as compared to females in both the age groups as well as collectively.
2. In the age group of 40-60 years, the distance between genu and fornix was 2.70 cm in males and 2.27 cm in females, the difference being statistically highly significant.

There was no statistical difference in the measurements of splenium between males and females.

(b) MRI scans: The mean values of CC parameters and the comparison between the two sexes along with p values are shown in Table 2. The major differences, which attained statistical significance, were:

Table-3: Age related changes in preserved brains

A. Males:

Parameter	20-40yrs (Mean age: 26.2 yrs)	40-60yrs (Mean age: 47.3yrs)	p value
G-F	2.18+/-0.33	2.70+/-0.41	0.00392
O-P	5.45+/-0.39	5.90+/-0.47	0.02961
WBA	0.91+/-0.12	0.72+/-0.17	0.00712
B. Females:			
Parameter	20-40yrs (Mean age: 28.2 yrs)	40-60yrs (Mean age: 45.2 yrs)	alue
Hc	1.68+/-0.48	2.18+/-0.43	0.01792
Wmi	0.37+/-0.11	0.46+/-0.08	0.04300

All measurements are in centimeters.

- WBA: Maximum width of anterior half of CC body (excluding genu).
- O-P: Distance from occipital pole of brain to posterior most point of CC.
- G-F Length: Distance between anterior edge of genu to anterior edge of columns of fornix.
- Hc: Height of corpus callosum.
- Wmi: minimum width of body of CC.

1. Lc (length CC), LB (length brain), G-F (genu-fornix distance), distances between the anterior most and posterior most points to the corrtical surfaces(A-S, P-S), F-A (distances between frontal pole and anterior most point of CC) and O-P (distance from occipital pole of brain to posterior most point of CC) were greater in males.
2. Splenial width was more in older females (1.43 cm) as compared to older males (1.18 cm).

Age related changes

(a) Preserved brain specimens: Observed values were arranged according to age and divided into two groups of 20-40 years and 40-60 years (Table3).

Males: Of the various parameters studied only the following reached any statistical significance:

1. G-F (distance between genu and fornix) and O-P (distance from occipital pole of brain to posterior most point of CC) were significantly more in older age group.
2. WBA (maximum width of anterior half of body of CC) was more in younger age group. All the ratios in both the groups were, however, similar.

Females: The statistically significant age related changes were:

1. Height of CC (Hc) and 2. Minimum width of CC (Wmi), were more in older age group as compared

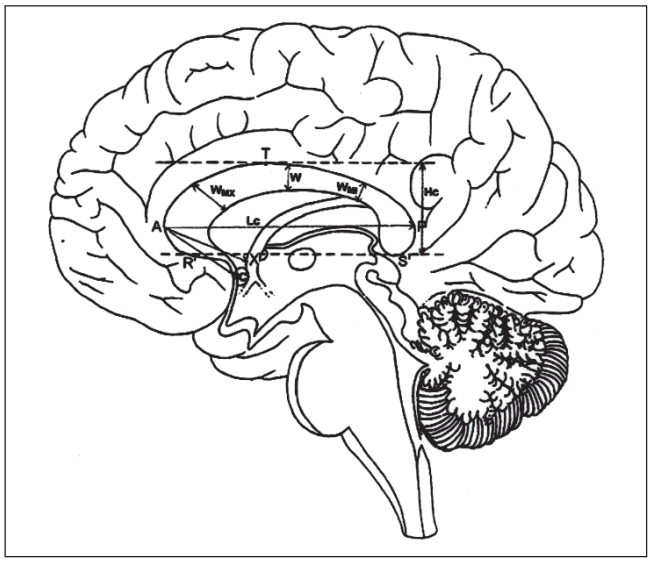

Fig 3: Measurements of corpus callosum (I).

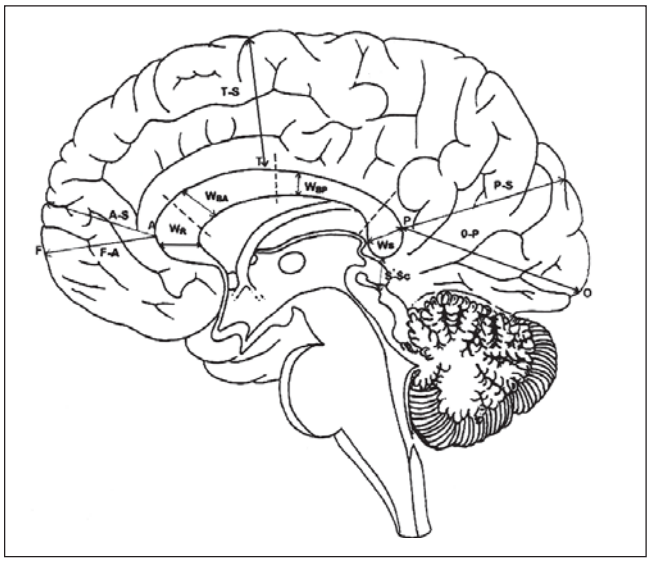

Fig 4: Measurements of corpus callosum (II).

Table-4: Age related changes (MRI scans)

A. Males:

Parameter	20-40yrs (Mean age: 29.8 yrs)	40-60yrs (Mean age: 48.4yrs)	p value
G-F	2.90+/-0.27	3.19+/-0.28	0.03284
B. Females:			
Parameter	20-40yrs (Mean age: 28 yrs)	40-60yrs (Mean age: 55 yrs)	alue
Wr	0.96+/-0.12	1.21+/-0.22	0.03277
Ws	1.07+/-0.11	1.43+/-0.13	0.00113
Ws/LB	0.070+/-0.01	0.10+/-0.01	0.00305
Ws/Lc	0.15+/-0.02	0.20+/-0.02	0.00405

All measurements are in centimeters.

- G-F Length: Distance between anterior edge of genu to anterior edge of columns of fornix.
- Wr: Maximum width of rostrum.
- Ws: Maximum width of splenium.
- Ws/LB: Splenial width / length of brain.
- Ws/LC: Splenial width / length of CC.

to younger females. Again the ratios (except W/Lc) were same in both the groups.

(b) MRI scans (Table 4):

Males: Among various parameters measured, only G-F was significantly greater in the older (40-60 years) age group.

Females: Statistically significant differences were seen in the following CC parameters only:

1. Width rostrum (Wr) and width splenium (Ws) were greater in older females
2. Ws/LB and Ws/Lc were more in older females as compared to younger age group.

DISCUSSION

CC has been the focus of fair amount of research and debate, especially its morphology in relation to age and sex. In recent years, most of the available studies have been carried out on MRI scans [2,3,6,9,11-13,15,17-20] while relatively few studies are based on formalin-fixed autopsy brain specimens.[1,2,4,7,16]

Gender related differences: Review of various studies available show that sexual dimorphism has been reported in different parts of CC but there is no consistent parameter that is constant in all studies. Witelson[7] studied sex differences in the isthmus and genu and concluded that total callosum, genu and anterior mid-body were greater in absolute area in males. On the other hand, isthmus was significantly larger in females. Takeda *et al*. [20] reported no sexual difference in the measurements of CC in Japanese subjects.

In this study most of the CC parameters were found to be similar in both sexes in both the autopsy and the MRI group. Most striking was the variations in callosal measurements in all these groups regardless of age or gender. Sex related differences were however, observed in the following parameters:

1. Larger CC length in males as compared to females in the MRI group. This is possibly related to larger brain size in males. A longer CC in males was also reported by Suganthy *et al*[17] and Elster *et al*.[18]
2. The width of the anterior half of CC decreased with increasing age in males, but not in females in preserved brains. Suganthy *et al*[17] also reported similar findings on width of genu and trunk in males in MRI study but these changes were not observed in MRI group in the present study.
3. Another sexual dimorphism evident in our study of preserved brains was greater S'-Sc distance in males (across all age groups).

Some studies have reported greater width of trunk in females, larger isthmus in females[7,21], larger genu in males[7,16] and a larger anterior trunk in males.[7] These findings were not observed in our study, nor have they been consistently reported in other studies. In fact, most studies have failed to find any evidence of sexual dimorphism in CC.

Sexual dimorphism in splenium: The splenium has received more attention than any other part of CC in almost all studies on sexual dimorphism. Some studies have reported greater splenial width and area in

females.[1,3-5,22] Bishop and Wahlstein,[8] on the basis of 19 independent studies of human CC, concluded that there is insufficient evidence to support the presence of sex related differences in the size or shape of the splenium, irrespective of difference in the over all brain size in the two sexes. Luders *et al*[9] also suggested that effect of individual variations in callosal size was large enough to out range any effect of splenial size differences between males and females. In some studies males tended to have larger splenial area although the difference never reached statistical significance. Witelson[7] also did not report any sex related differences in splenial areas, either in absolute size or size proportional to brain weight. Similarly, the Japanese[20] and Indian[16,17] studies also failed to find gender related difference in splenium. In the present study no significant difference in splenial width between males and females was found in both the groups. This was in agreement with most of the literature. On further subgroup analysis in MRI group splenial width in older females (40-60 year of age) was found to be more than the older males. In this group, the splenial width also increased with age in females whereas no such change was noticed in males. However, since this gender related differences in splenial width were observed only in the MRI group and not in the preserved brains, its significance remains to be explored. Possibly more refined measure of splenial shape and size may be necessary to finalize the question of gender differences in splenial morphology. However, on the basis of the findings in the present study, one can conclude that there is no significant sexual dimorphism in splenium. Variations observed are more likely to be a function of individual differences regardless of sex.

Age related changes in CC morphology: Changes in callosal size in aging adults are controversial. Although many studies have concluded that age related callosal thinning is modest[6,14,23,24] some studies have reported that it is statistically significant.[13,15,26] Most cross sectional MRI studies of the CC fail to show age related shrinkage in adults from 3rd-7th decade.[14,23,25] In contrast some studies[13,15] have shown senescent effects over 3rd-8th decades. Others[5,19] have found age effects in elderly subjects especially those exceeding 55 years. A few studies[15,19] have shown greater vulnerability to aging in anterior than posterior regions of CC. This is particularly marked in women.[19] while some have found greater vulnerability of men compared to women in older decades.[24] Sullivan *et al*[26] reported statistically significant thinning of genu, body and splenium with age on MRI study of mid sagittal brain sections. As the CC is located adjacent and superior to the lateral ventricle, these changes have been speculated to be due to lateral ventricle expansion in elderly.[19,26]

Weis *et al*[15] have reported significant decrease in genu and anterior part of the trunk with age, suggesting alteration in frontal and temporal inter-hemispheric fibre system. Decrease in callosal size may reflect a sex related difference in histological changes in cerebrum, such as the loss of synaptic connections and callosal collaterals. A different or earlier aging process may occur in the brains of men than in woman. Salat *et al*[19] reported that among elderly subjects (age range 65-95yrs) age related atrophy of the anterior and middle sectors of the CC occurred in women but not in men. They concluded that men and women may show different time course of CC development and age related loss. They postulated that men might show atrophic changes before women while these changes occur in women late in life.

In the present study, the width of the anterior half of the CC was more in younger males than in older males i.e. the CC width decreased with age in males, but not in females (preserved brain group). Suganthy *et al*[17] also reported similar findings in MRI study. Witelson[7] observed that the callosal size decreased with chronological age in males. Others have also documented that men exhibit maximum callosal width in their early 20's with a relatively rapid decline thereafter.[27,28] The decrease in the width of CC with age in the present study is consistent with reported decline in dichotic listening and binaural processing skills with age occurring earlier in men than in woman by Bellis and Wilber.[28] This is possibly related to atrophic changes in the brain which are more notable in males. In females of preserved brain group, the height of the CC increased with age. Reduction in callosal width with age and an increase in height of CC with age have been reported by Takeda *et al.*[20]

In the MRI group, the distance G-F increased with age in males, a finding which was noted in the preserved brain group also. The possible explanation could be atrophic changes with age leading to ventricular dilatation. This age related changes were not consistently same in both the groups studied. Apart from the differences noted above, none of the other parameters showed any age related variation.

Corpus callosum, being the major structure connecting both the hemispheres, is likely to be affected by the physiologic as well as pathological changes occurring in the cortical and sub cortical regions of brain. Therefore different sub regions of the CC may be affected depending upon the region of the brain involved, as fiber systems connecting corresponding hemispheric regions pass through specific callosal sub regions. Therefore, alteration in CC morphology may give a clue towards diagnosis of specific disease processes. A knowledge

of CC morphology and the gender as well as age related changes, thus is likely to be helpful in providing baseline data for the diagnosis of presence and progression of disease.

In the present study, sexual dimorphism was not observed in most of the CC parameters studied. No gender related difference was found in the splenium as well. Although there were many differences in various parameters studied most striking finding was the variations in callosal shape and size among individuals regardless of age and gender. Therefore, it might not be correct to attribute differences in hemispheric functions between sexes to callosal connections. Age related thinning of the CC was observed in width of anterior half of CC, but only in males. This is possibly related to atrophic changes in the brain which are more notable in males. The distance G-F also increased with age in males, again secondary to ventricular dilation which occurs following brain atrophy. These structural alterations could well be the basis of gender related decline in certain cognitive functions with age.

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