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Sex Differences in the Corpus Callosum of the Living Human Being

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The sexual dimorphism of the corpus callosum has remained controversial since the original report by de Lacoste-Utamsing and Holloway in 1982, for several reasons: (1) measurements have been performed in a variety of ways in different laboratories, in part because published reports frequently do not describe the methodology in detail; (2) despite known age-related changes during both childhood and adulthood, no investigators have explicitly age-matched subjects; and (3) the size and shape of corpora callosa vary considerably among individuals, requiring large sample sizes to demonstrate significant sex differences. Therefore, we have examined magnetic resonance images for 24 age-matched children and 122 age-matched adults for possible sex differences in the corpus callosum. While we observed a dramatic sex difference in the *shape* of the corpus callosum, there was no conclusive evidence of sexual dimorphism in the *area* of the corpus callosum or its subdivisions. Utilizing several criteria, there were significant sex differences in shape: subjective evaluation indicated that the posterior region of the corpus callosum, the splenium, was more bulbous shaped in females as a group and in women, and more tubular-shaped in males as a group and in men; mathematical evaluation confirmed this observation in that the maximum width of the splenium was significantly greater in women than in men, and that the percentage by which the average width of the splenium was greater than that of the adjacent corpus callosum was significantly greater in females than in males. However, sex differences in bulbosity did not reach significance in children (aged 2–16 yr). In contrast, among the area measurements of the corpus callosum and 22 subdivisions, only 1 exhibited a significant sex difference, which would be expected by chance. The area of the corpora callosa increased significantly with age in children and decreased significantly with age in adults. In adults, the midsagittal surface area of the cerebral cortex decreased significantly with age in women but not in men. These anatomical sex differences could, in part, underlie gender-related differences in behavior and neuropsychological function.

The possibility that neuroanatomical sex differences underlie functional sex differences has been studied extensively in nonhuman animals. In regions of the CNS known to control sex-related behaviors, sexual dimorphisms range from subtle differences in the size of individual neurons (Pfaff, 1966), dendritic branching patterns (Greenough et al., 1977), and synaptic organization (Raisman and Field, 1971), to dramatic dimorphisms in the volumes of cell groups (Nottebohm and Arnold, 1976; Gorski et al., 1978). In addition, several sexual dimorphisms have been found in regions not necessarily involved in reproductive function. For example, in rats, there are sexually dimorphic patterns of cortical and hippocampal asymmetries (Diamond et al., 1983). While several neuroanatomical sexual dimorphisms are influenced by perinatal environmental factors, nearly all identified sex differences are known to be influenced by gonadal hormones perinatally and/or during adulthood.

In contrast to what is known in laboratory animals, there are relatively few reported sex differences in the human CNS. In regions possibly influencing reproductive function, there are several sex differences: relatively marked sexual dimorphisms exist in cell groups in the preoptic–anterior hypothalamic area (Swaab and Fliers, 1985; Allen et al., 1989), a region that has been implicated in rodents and subhuman primates in gonadotropin release (Gorski, 1968; Plant et al., 1979), maternal behavior (Jacobson et al., 1980), and sexual behavior (Robinson and Mishkin, 1966); similarly, a region of the bed nucleus of the stria terminalis is larger in males than in females (Allen and Gorski, 1990), the shape of the suprachiasmatic nucleus differs between men and women (Swaab et al., 1985), and Onuf's nucleus in the spinal cord, which innervates perineal muscles, contains more motoneurons in the male than in the female (Forger and Breedlove, 1986).

Recent reports suggest that sex differences in nonreproductive functions in humans may also have a neuroanatomical basis. Such functional sex differences may include the following: (1) cognitive decline with advancing age (Tomlinson and Corsellis, 1984); (2) subtle differences in cognitive skills whereby women generally perform better on verbal measures and men perform better in spatial and mathematical skills (Harris, 1978; Kimura, 1987); (3) a prevalence in boys relative to girls of a variety of developmental language disorders including delayed speech acquisition, dyslexia, infantile autism, and stuttering (Hier, 1979); and (4) greater functional asymmetry in the male than in the female brain (McGlone, 1980; Beaton, 1985; Kimura, 1987). Several structural sexual dimorphisms suggest that there may be a morphological basis for these functional differences. Moreover, possible gender differences in cognitive decline with age could correspond with age-related sex differences in decreases

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in brain size (Hatazawa et al., 1982; Hubbard and Anderson, 1983). In men, just as there appears to be greater functional asymmetry, there is greater morphological brain asymmetry in the temporal planum (Wada et al., 1975). In women, there may be greater connectivity between the 2 hemispheres of the brain: the massa intermedia of the thalamus is more often present (Rabl, 1958), and both the massa intermedia (Allen and Gorski, 1987) and the anterior commissure (Allen and Gorski, 1986) are larger at the midsagittal plane in women than in men. Similarly, sex differences in the corpus callosum (CC) were originally reported by de Lacoste-Utamsing and Holloway (1982), but have subsequently become controversial. This is the first study that replicates each of the 4 original measurements of de Lacoste-Utamsing and Holloway (1982), uses age-matched male and female subjects, and contains the largest sample size to date. In addition, the CC has been examined extensively for sex differences in its shape and the area of many regional components.

Materials and Methods

We examined the magnetic resonance images (MRIs) of the midsagittal plane of each human brain that was scanned at 4 southern California MRI centers before locating a center that had enough midsagittal images from subjects who had "normal" scans according to the radiologists' reports to obtain a minimum of 100 age-matched male and female subjects. All images in this study were taken at the University of California at Irvine Medical Center using a headcoil of a Technicare Teslacon 2.0-tesla superconductive magnet operating at 0.6 tesla. Each single-echo midsagittal acquisition was 0.75 cm thick and obtained for T1 or T2 weighting.

From approximately 1000 sets of MRIs of the brains of human beings, each set of which contained a midsagittal section, 246 midsagittal images were selected, without knowledge of age or gender, on the basis of the following: (1) precision of the midsagittal plane determined by the callosal sulcus separating the CC from the cingulate gyrus, the appearance of the cerebral aqueduct between the tectum and tegmentum, the V-shaped roof of the fourth ventricle, the presence of the cerebellar vermis, and the complete absence of the cerebellar hemispheres; (2) quality of image such as freedom from any head motion during imaging; and (3) general absence of neuropathology determined by a "normal" MRI according to the radiologist's report and no history of neuroendocrine abnormality, neurosurgery, or previous diagnosis of a neurological disorder known to affect gross neural structure. Although most subjects, except for several controls, were scanned for a medical reason, a majority of which included sinusitis, headache, dizziness, sensory problems, fainting, and nausea, there is no reason to believe that these problems would influence neural structure detectable by an MRI that appeared "normal." Subsequently, without reference to the image itself, the MRI codes of these 246 individuals, with their sex and age, were separated into 2 columns based on gender and ordered according to age. Since not all subjects were paired, due to age and sex discrepancies, this resulted in 73 age-matched pairs with no more than 5 yr between any pair. Using age 16 as the beginning of adulthood, these subjects were separated into 12 pairs of children and 61 pairs of adults.

The midsagittal images from each of the 146 individuals, as well as a standard grid used for evaluating magnification, were photographed and made into slides (Fig. 1*A,B*). The images were projected at a magnification of either 1.225× or 4× onto a flat projection surface covered by white drawing paper. To avoid distortion of the midsagittal surface of the brain, correct alignment of the slide projector with the projection surface was achieved by measuring the squares of the grid in different regions on the projection surface and making minor adjustments in the position of the projector, until the sides of the squares of the grid were of equal length when projected.

Without knowledge of age or sex, 2 individuals first traced each image of the midsagittal surface of the brain, which included the cerebral cortex, CC, cerebellum, midbrain, pons, and medulla, at a magnification of 1.225×. Because the curved and convoluted outer surface of the cerebral cortex frequently did not have clearly defined borders, its boundary was determined by the relatively distinct dura mater. Subsequently, the projector was realigned at a magnification of 4×, and the midsagittal outline of the CC was drawn.

Each investigator made 2 photocopies of the drawings of the CC. The first set of drawings was evaluated by dividing the CC using the "straight-line method" (S-L method; Fig. 1*C,E*), which took into account the distance from the most rostral to the most caudal point of the CC along a straight line. This straight line was used to divide the CC into fifths [from anterior to posterior: anterior ⅕ (A5), 2nd ⅕, 3rd ⅕, 4th ⅕, and posterior ⅕ (P5)], anterior half (A2), posterior half (P2), posterior third (P3), and posterior fourth (P4), by drawing lines perpendicular to the straight line. The second set of drawings was analyzed by the "curved-line method" (C-L method; Fig. 1*D, F*), which measured the length of the curved line bisecting the ventral and dorsal halves of the CC from the rostrum to the splenium. This curved line was obtained by drawing adjacent lines, at intervals of no more than 2 mm apart, as perpendicularly as possible between the ventral and dorsal surface of the CC, determining the midpoint of each line, and connecting these midpoints to obtain the curved, bisecting line. The length of this curved line was measured using the Bioquant Hipad digitizer (Bioquant IBM version 2.1, R & R Biometrics), which had a resolution of 0.5 mm. Similarly, this curved line was divided into each ⅕, A2, P2, P3, and P4 by drawing lines perpendicular to the tangent of the bisecting line. From these measures, the areas within P2 minus P3 (P2 − P3) and P3 − P5 were calculated using both the S-L and C-L methods of partitioning. P2 − P3 and P3 − P5 were quantified because they may contain axons from asymmetric regions of the cerebral cortex and have been found to differ between men and women in relation to hand preference (Witelson, 1986, 1989).

We evaluated the shape of the posterior CC for possible sex differences, utilizing 3 criteria: (1) subjective classification of gender based on the shape of the posterior CC, (2) maximum splenium width (MSW), and (3) bulbosity coefficients.

(1) To determine whether the CC could be evaluated subjectively acccording to gender, based on reports of a more bulbous-shaped female splenium and a more tubular-shaped male splenium, 3 investigators, without knowledge of the subjects' gender, divided the CC drawings into male and female groups. The subjects' gender was based on the classification by a minimum of 2 of the investigators.

(2) Because the CC is a continuous structure without defined internal dimensions, and because the splenium is nonspecifically defined as the "thickened posterior extremity of the CC," we considered P5 of the CC to be the splenium (de Lacoste-Utamsing and Holloway, 1982). The MSW was determined by finding the maximum distance perpendicular to the tangent of the bisecting line in the P5 of the CC (Fig. 1*E*). Similarly, the minimum width of the body of the CC was determined by finding the minimum distance perpendicular to the tangent of the bisecting line anterior to P5 and posterior to the rostrum.

(3) To quantify the bulbosity of P5, we utilized a "bulbosity coefficient." This is a measure that compares the average width of the splenium with the average width of an adjacent region of the CC. Specifically, the bulbosity coefficient is the percentage by which the average width of P5 is wider, or more "bulbous," than the average width of the adjacent CC. To derive the bulbosity coefficient, we first obtained the average width of a region by dividing its area by the length of the curved line coursing through it. For example, the average width of P5 is the area of P5 divided by the length of the C-L through P5. Second, we subtracted the average width of the adjacent region from the average width of P5 and divided by the width of the adjacent region. This number was multiplied by 100 to obtain the percentage. For example, the bulbosity coefficient for P5 in relation to P2 is calculated as follows:

$$[(\text{average width of P5} - \text{average width of P2 not including P5})/(\text{average width of P2 not including P5})] \times 100$$

We obtained bulbosity coefficients for P5 in relation to the adjacent ⅕ (4th ⅕), P2, and the CC.

Both investigators quantified the area of the cerebral cortex, CC, and the components of the CC in both their S-L- and their C-L-partitioned set of drawings, using the Bioquant Hipad digitizer. In addition, each investigator measured the MSW, minimum width of the body, and both the straight length and the curved length of the CC. Each measurement of the 2 investigators was compared, and if there was a difference of greater than 5% between measurements, the appropriate region(s) of the CC was reexamined by a third person and the 2 measurements in closest agreement were utilized. Each of these pairs of measurements was averaged.

For both children and adults, each measurement was examined for changes with advancing age using Pearson's correlation coefficient (Daw-

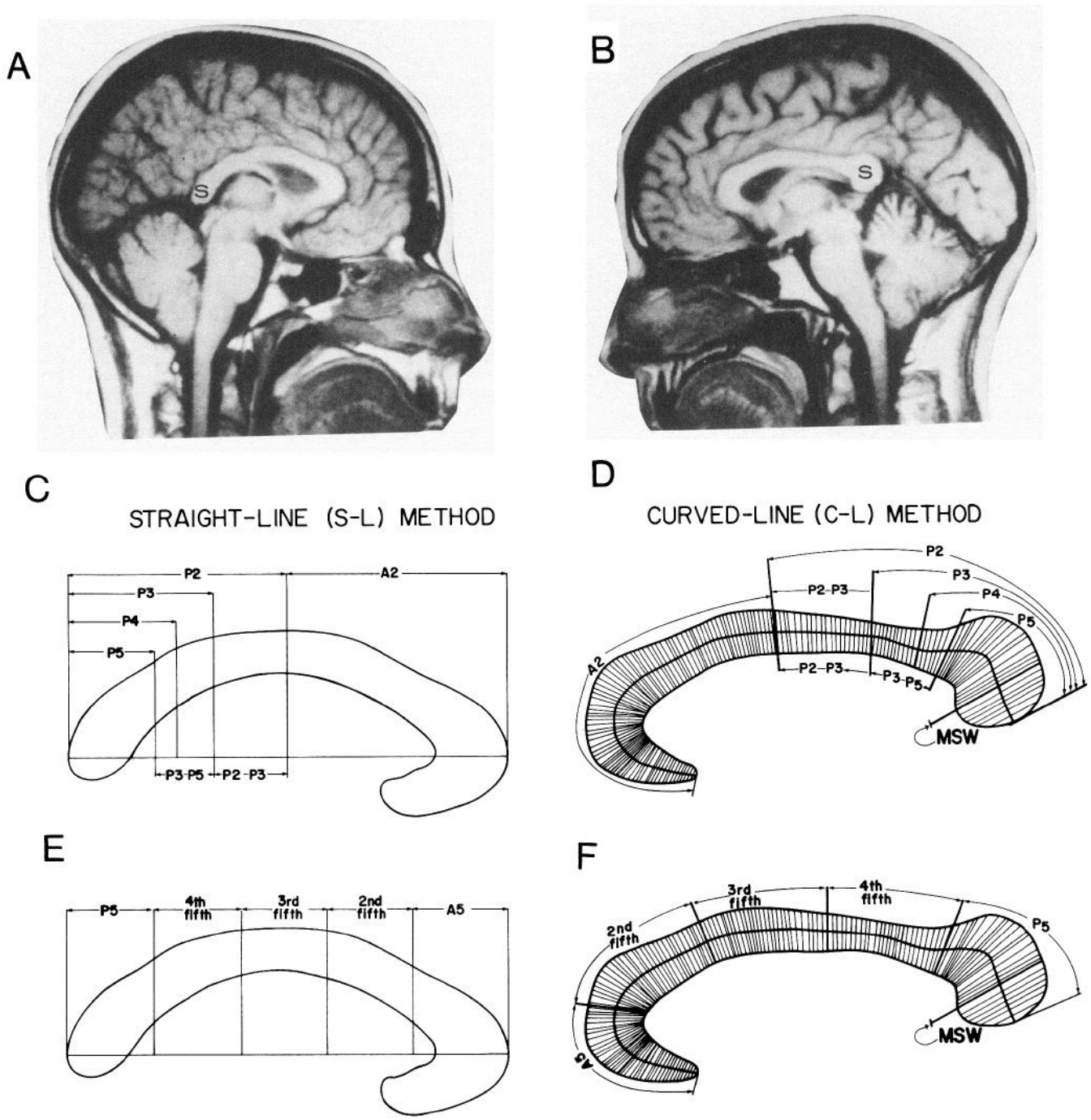

Figure 1. Sexual dimorphism in the splenium of the CC. *A* and *B* are MRIs of the midsagittal section of the human CC from a male (*A*) and a female (*B*), illustrating a more tubular-shaped male splenium (*S*) and a more bulbous-shaped female splenium (*S*), respectively. *C* and *E*, tracings of the CC from *A*, illustrate the S-L method of partitioning. *D* and *F*, tracings of the CC from *B*, illustrate the C-L method of partitioning and the method of obtaining the MSW.

son-Saunders and Trapp, 1990). Each measure was further examined for girls, boys, women, and men separately, and stepwise regression was used to determine whether the regression slopes differed between girls and boys and between women and men. The cerebral cortex was of particular interest in this respect because we had originally planned to account for sex differences in brain size by adjusting our measurements of the CC to the area of the cerebral cortex, though this was not possible because of a difference in regression slopes between women and men (see Results). Measurements of the CC were examined using the paired *t* test, and subjective classification of gender based on the shape of the posterior CC was examined with χ^2. Because only 1 of the 23 area measurements of the CC and its subdivisions exhibited a significant sex difference, which would be expected by chance, we evaluated it (P2 – P3) with the Bonferroni *t* method for multiple comparisons (Dunn's multiple-comparison procedure; Dawson-Saunders and Trapp, 1990).

Results

The present results are based on an analysis of the brains of 73 age-matched pairs of males and females (Tables 1–3). Among the children, the age range in years for girls was 2 to 15 (Mean

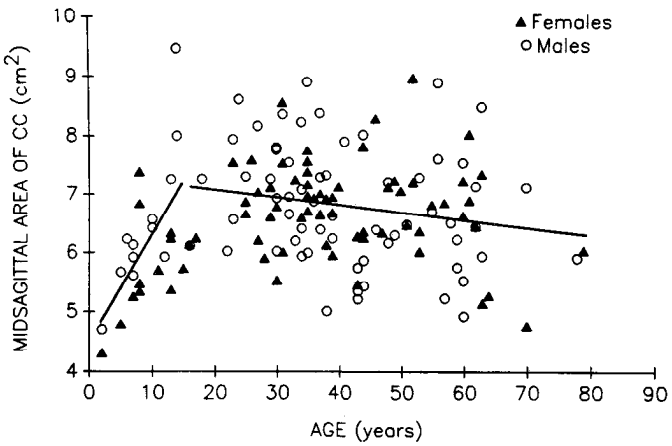

Figure 2. Midsagittal area of the CC in relation to age. The area of the CC and age are correlated for both children (2–15 yr of age; $r = 0.60$; $p = 0.0019$) and for adults (16–79 yr of age; $r = 0.19$; $p = 0.032$). There was no significant difference in regression slopes between boys and girls or between men and women. The *ascending* and *descending lines* represent the regression slopes for children and adults, respectively.

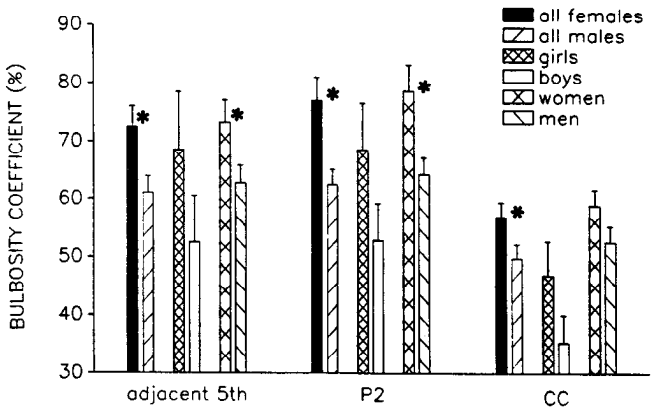

Figure 3. The bulbosity coefficients, which represent the percentage by which the splenium (P5) of the CC is wider, or more "bulbous," than the adjacent regions of the CC, are compared between females and males, between girls and boys, and between women and men. The *adjacent fifth* compares the splenium with the 4th ⅛ of the CC, *P2* compares it to the remaining posterior half, and *CC* compares it to the remaining CC. *Asterisks* denote significant differences ($p < 0.05$; see Table 3).

± SEM = 9.25 ± 3.8) and for boys was 2 to 14 (8.9 ± 3.8), with an average absolute difference between pairs of 1 yr. Among adult subjects, the age range in years for men was 16 to 78 (42.1 ± 14.0) and for women was 16 to 79 (41.9 ± 13.6), with an average difference between pairs of 1.2 yr.

Correlation between measurements

Throughout this study, there was a highly significant correlation between each measurement of the 2 experimenters ($P < 0.0001$).

Whether we examined males and females separately or as a group, when comparing the area of the various subdivisions of the CC utilizing the S-L and the C-L method, there was a significant difference between each measurement except for P4. The regions A2, A5, and P5 were significantly larger in area when defined by the S-L method than by the C-L method, whereas the 2nd, 3rd, and 4th ⅛, as well as P2, P3, P2 − P3, and P3 − P5, were greater when defined by the C-L method than by the S-L method. However, no trend was observed for either method to increase the probabilities of significant sex differences (Table 2).

Changes with advancing age

We examined children and adults separately for age-related changes in the cerebral cortex, the entire CC, and 22 components of it. Among the children, the CC and each of its regions *increased* significantly with advancing age (Table 3); however, the increase was not significant in the midsagittal area of the cerebral cortex. When regression slopes were compared between girls and boys, A5 ($p < 0.05$), 2nd ⅛ ($p < 0.05$), 3rd ⅛ ($p < 0.02$), and A2 ($p < 0.02$), utilizing *both* the S-L and the C-L methods of partitioning, exhibited significantly greater increases with advancing age in boys than in girls. In adults, the areas of the CC, A5, 2nd and 3rd ⅛, and A2, *decreased* significantly with advancing age. The only measure that exhibited significantly different regression slopes between women and men was the midsagittal area of the cerebral cortex that, though decreasing insignificantly in adults as a group ($r = 0.065$; $p = 0.477$), decreased significantly in women ($r = -0.268$; $p = 0.037$) but not in men ($r = 0.1038$; $p = 0.426$).

Table 1. Mean ± SEM for measurements of the cerebral cortex, CC, MSW, minimum body width, and bulbosity coefficients

	All subjects		
	Males	Females	*p*
Cerebral cortex (cm²)	93.64 ± 0.73	89.93 ± 0.65	0.002*
CC (cm²)	6.81 ± 0.09	6.63 ± 0.07	0.26
MSW (cm)	1.25 ± 0.02	1.30 ± 0.02	0.12
Minimum body width (cm)	0.52 ± 0.01	0.50 ± 0.01	0.15
Bulbosity coefficients			
Splenium relative to 4th ⅛ (%)	61.0 ± 2.9	72.4 ± 3.6	0.015*
Splenium relative to P2 (%)	62.4 ± 2.7	76.9 ± 4.0	0.002*
Splenium relative to CC (%)	49.7 ± 2.5	56.9 ± 2.5	0.033*

Data are presented as mean ± SDM; *p*, probability using the paired *t* test.

Table 2. Mean ± SEM for measurements of the CC with the S-L and C-L methods

	All subjects			Adults			Children		
	Males	Females	*p*	Men	Women	*p*	Boys	Girls	*p*
S-L method									
Length (cm)	7.18 ± 0.04	7.14 ± 0.04	0.63	7.24 ± 0.04	7.18 ± 0.04	0.46	6.86 ± 0.09	6.96 ± 0.08	0.50
P5 (cm^2)	1.88 ± 0.03	1.90 ± 0.03	0.77	1.92 ± 0.03	1.96 ± 0.03	0.55	1.67 ± 0.08	1.58 ± 0.06	0.46
P4 (cm^2)	2.17 ± 0.03	2.18 ± 0.03	0.91	2.22 ± 0.03	2.25 ± 0.03	0.65	1.91 ± 0.09	1.81 ± 0.07	0.81
P3 (cm^2)	2.55 ± 0.04	2.54 ± 0.04	0.83	2.61 ± 0.04	2.62 ± 0.04	0.83	2.29 ± 0.10	2.12 ± 0.09	0.28
P2 (cm^2)	3.30 ± 0.04	3.24 ± 0.04	0.42	3.36 ± 0.05	3.34 ± 0.04	0.80	3.01 ± 0.13	2.73 ± 0.11	0.16
A2 (cm^2)	3.43 ± 0.05	3.35 ± 0.04	0.35	3.42 ± 0.05	3.42 ± 0.04	0.98	3.49 ± 0.13	3.00 ± 0.09	0.05*
P2 − P3 (cm^2)	0.75 ± 0.02	0.70 ± 0.02	0.06	0.75 ± 0.02	0.72 ± 0.02	0.19	0.72 ± 0.05	0.61 ± 0.04	0.08
P3 − P5 (cm^2)	0.67 ± 0.01	0.64 ± 0.01	0.19	0.68 ± 0.02	0.66 ± 0.01	0.46	0.62 ± 0.03	0.54 ± 0.03	0.11
C-L method									
Length (cm)	9.10 ± 0.06	9.04 ± 0.05	0.57	9.16 ± 0.07	9.09 ± 0.05	0.57	8.78 ± 0.11	8.78 ± 0.11	1.00
P5 (cm^2)	1.84 ± 0.03	1.86 ± 0.03	0.63	1.88 ± 0.03	1.92 ± 0.03	0.40	1.64 ± 0.08	1.54 ± 0.07	0.38
P4 (cm^2)	2.17 ± 0.03	2.18 ± 0.03	0.85	2.22 ± 0.04	2.25 ± 0.03	0.57	1.93 ± 0.08	1.81 ± 0.08	0.33
P3 (cm^2)	2.62 ± 0.04	2.61 ± 0.04	0.86	2.67 ± 0.04	2.69 ± 0.04	0.78	2.37 ± 0.10	2.19 ± 0.09	0.25
P2 (cm^2)	3.54 ± 0.05	3.46 ± 0.05	0.32	3.60 ± 0.05	3.57 ± 0.04	0.72	3.26 ± 0.14	2.93 ± 0.11	0.12
A2 (cm^2)	3.19 ± 0.04	3.12 ± 0.04	0.41	3.19 ± 0.05	3.19 ± 0.04	0.96	3.20 ± 0.12	2.79 ± 0.08	0.09
P2 − P3 (cm^2)	0.92 ± 0.02	0.85 ± 0.02	0.01**	0.93 ± 0.02	0.88 ± 0.02	0.08	0.90 ± 0.06	0.74 ± 0.04	0.04**
P3 − P5 (cm^2)	0.78 ± 0.01	0.75 ± 0.01	0.12	0.80 ± 0.01	0.77 ± 0.01	0.30	0.73 ± 0.04	0.65 ± 0.03	0.18

Data are presented as mean ± SEM; *p*, probability using the paired *t* test. For simplicity, the means for A5, 2nd ⅛, 3rd ⅛, and 4th ⅛ are not given; however, none exhibited sexual dimorphism. *, $p = 0.052$, NS.

Size of the CC

Although the overall area of the CC was slightly greater in men than in women (1.0%; $p = 0.68$) and in boys than in girls (12.5%; $p = 0.102$; Table 1, Fig. 2), this difference was considerably less than the reported sex differences in brain weight (de Lacoste-Utamsing and Holloway, 1982). The CC ranged from 4.31 to 8.97 cm^2 for females and from 4.70 to 9.474 cm^2 for males; hence, there was considerable overlap in the size of the CC between the male and female subjects.

Sex differences in the shape of the CC

There were striking sex differences in the shape of the splenium, utilizing 3 criteria for evaluation: (1) subjective classification of the gender based on the shape of the posterior CC, (2) MSW, and (3) bulbosity coefficients.

(1) Subjective classification of the posterior CC of all subjects by sex based on a more bulbous-shaped female splenium and a more tubular-shaped male splenium revealed a significant correlation between the observers' sex rating based on shape and the actual gender of the subject ($\chi^2 = 13.2603$; 1 df; contingency coefficient = 0.289; $p < 0.0003$). Specifically, 80 out of 122 (66%) of the adults' CC ($\chi^2 = 10.623$; 1 df; contingency coefficient = 0.283; $p < 0.0011$) and 16 out of 24 (67%) of the childrens' CC ($\chi^2 = 1.500$; 1 df; contingency coefficient = 0.243) were correctly identified; however, this is not more accurate than could be achieved by chance ($p < 0.2207$).

(2) The degree of bulbosity or tubularness of the splenium was ascertained as in the original study (de Lacoste-Utamsing and Holloway, 1982) by measuring the MSW (Table 1). We found that the MSW was significantly greater in women than in men both before ($p = 0.035$) and after ($p = 0.01$) the area of the CC was considered. However, in children, there was no significant sex difference in MSW; though its absolute value was greater in boys than in girls, its value adjusted for CC area was greater in girls.

(3) The bulbosity coefficients, which represent the percentage by which the average width of the splenium is greater than the

Table 1. Continued

Adults			Children		
Men	Women	*p*	Boys	Girls	*p*
92.96 ± 0.77	88.57 ± 0.69	0.006*	97.09 ± 1.95	92.98 ± 1.67	0.2
6.87 ± 0.10	6.80 ± 0.07	0.68	6.49 ± 0.26	5.76 ± 0.18	0.1
1.27 ± 0.02	1.35 ± 0.02	0.035*	1.14 ± 0.035	1.07 ± 0.04	0.16
0.53 ± 0.01	0.52 ± 0.01	0.63	0.51 ± 0.02	0.42 ± 0.02	0.01*
62.7 ± 3.1	73.2 ± 3.8	0.038*	52.5 ± 8.0	68.5 ± 9.9	0.23
64.3 ± 2.9	78.6 ± 4.5	0.006*	52.9 ± 6.3	68.5 ± 8.0	0.17
52.6 ± 2.7	58.9 ± 2.7	0.09	35.3 ± 4.7	46.8 ± 5.9	0.16

Table 3. Correlation coefficients for changes with advancing age

	Children		Adults	
	r	*p*	*r*	*p*
Area of cerebral cortex	0.074	0.73	0.06	0.472
Area of CC	0.601	0.0019*	−0.19	0.032*
MSW	0.639	0.0008*	0.012	0.897
Minimum body width	0.504	0.012*	−0.037	0.682
Straight length	0.690	0.0002*	0.059	0.514
Curved length	0.580	0.003*	−0.025	0.784
Areas within the CC				
A5	0.454	0.026*	−0.218	0.016*
2nd ⅛	0.492	0.015*	−0.300	0.0008*
3rd ⅛	0.503	0.012*	−0.234	0.009*
4th ⅛	0.444	0.029*	−0.068	0.458
A2	0.498	0.013*	−0.298	0.0008*
P2	0.645	0.0007*	−0.067	0.462
P3	0.659	0.0005*	−0.046	0.612
P4	0.682	0.003*	−0.055	0.546
P5	0.712	0.0001*	−0.034	0.710

This table shows Pearson's correlation coefficients (*r*) and probabilities (*p*) for changes with advancing age. These values only represent areas of the CC that have been partitioned using the C-L method (see Fig. 1*D*); however, the corresponding S-L-partitioned areas exhibited similar values.

average width of adjacent regions of the CC, were all significantly greater in females than in males (Table 1, Fig. 3). Specifically, the bulbosity coefficient was 18.7% greater in females in relation to the adjacent ⅛ ($p = 0.015$), 23.2% greater in relation to the remaining posterior half ($p = 0.002$), and 14.5% greater in relation to the remaining CC ($p = 0.032$). These percentage differences were even greater for children: the bulbosity coefficient was 30.5% greater in girls in relation to the adjacent ⅛, 29.5% greater in relation to the remaining posterior half, and 32.6% greater in relation to the remaining CC. In contrast to males and females as a group, however, these values for children were not significant in the 2 sexes, perhaps because of the small sample size ($N = 12$ pairs).

Regional sex differences in the CC

Regions of the CC were examined using both the S-L and the C-L methods of partitioning in terms of each ⅕, P4, P3, P2, A2, P2 − P3, P3 − P5, the minimum body width, S-L length, and C-L length (Fig. 1, Table 2). The only region that exhibited sexual dimorphism was P2 − P3 examined by the C-L method, which was greater in males ($p = 0.01$) and boys ($p = 0.04$). However, because 23 measurements of area were compared, including the CC and 22 subdivisions, at least 1 significant difference would be expected by chance at the level of $p < 0.05$; therefore, we examined P2 − P3 utilizing the conservative Bonferroni adjustment, in which case P2 − P3 was not sexually dimorphic statistically. In addition, each of these regions was adjusted for CC area by dividing by the respective CC area (calculations not shown). Following this adjustment, the only significant sex difference observed was a greater P5 in females ($p = 0.033$) and a greater P2 − P3 in males ($p = 0.021$) when examined by the C-L method; however, these differences were no longer present following the Bonferroni adjustment. Interestingly, the cross-sectional area of the splenium (P5) and its value adjusted for CC area was insignificantly greater in women than in men, using both methods of measurement. In children, though the cross-sectional area of the splenium was greater in boys than in girls, its area adjusted for CC area was greater in girls than in boys, again using both the S-L and the C-L methods. Note, however, that none of these differences were statistically significant in children alone, even without the Bonferroni *t* method of adjustment for multiple comparisons.

Correlations between the CC and its components

There was a significant correlation between the area of the CC and each of its area subdivisions ($r > 0.7$; $p < 0.001$), in addition to each linear measure (the curved length, straight length, minimum distance, and MSW; $r > 0.42$; $p < 0.02$), for all subjects, adults, men, women, children, boys, and girls.

Discussion

Methodological considerations

It is unclear whether the S-L or the C-L method of analysis is more appropriate for consistently partitioning the CC into regions that are more similar in terms of topographical organization of projections from different cortical areas. However, the C-L method is necessary for evaluating the CC in terms of sex differences in shape. The CC was occasionally difficult to trace at the tip of the rostrum, and this may add to error in the C-L partitions, while affecting only the rostral S-L division. Although there were significant differences between the C-L and the S-L measurements in each region except for P4, these differences were in the same direction for both genders.

Changes with advancing age

In children, all examined regions of the CC increased significantly with advancing age (Table 3). Furthermore, the anterior regions of the CC increased to a significantly greater extent in boys than in girls; however, it is unclear whether the CC in boys actually grows more rapidly than in girls, or whether the significant difference between regression slopes for area changes with advancing age reflects the fact that the largest of the 146 CC was of the oldest boy.

In adults, the anterior regions of the CC (A2, A5, 2nd ⅛, and 3rd ⅛), which carry axons from the frontal, premotor, and motor cortices, decrease in area significantly with advancing age; however, these changes are not significant in the posterior regions of the CC, which contain fibers from the somesthetic, parietal, occipital, and temporal lobes. It is unclear why the midsagittal area of the cerebral cortex was the only parameter of those measured that exhibited significant differences in regression slopes between women and men. However, several studies report that a decrease in brain volume occurs earlier in women than in men (Hatazawa et al., 1982; Hubbard and Anderson, 1983). Furthermore, in Alzheimer's disease, there is both improvement of cognitive function in some women who are treated with estrogen (Fillit et al., 1986) and a significant loss of large neurons in the midfrontal cortex in women but not men (Terry et al., 1981).

Sex differences in the anatomy of the CC

Although the CC is the largest interhemispheric commissure, composed of about 200–350 × 10^6 fibers connecting the right and left cerebral hemispheres, the axons that constitute it come from only approximately 2% of all neocortical neurons (Berlucchi, 1981). Investigations in both humans and other primates suggest that most callosal fibers arise from the association cortex and project to a homotopic position on the contralateral hemi-

sphere. For example, in the human, both the superior parietal lobule and the occipital cortex give rise to fibers that course through the splenium (de Lacoste et al., 1985), which appear to serve in the interhemispheric transfer of visual information (Gordon et al., 1971; Gazzaniga and Freedman, 1973). Of similar functional interest is the posterior body of the CC (approximately P3 − P5 and P2 − P3; Witelson, 1989), which carries fibers connecting the posterior parietal and temporal regions of the 2 hemispheres involved in language function (monkey, Seltzer and Pandya, 1983; Cipolloni and Pandya, 1985; man, de Lacoste et al., 1985).

Discrepancies in the literature

Although several investigators have attempted to replicate the original report (de Lacoste-Utamsung and Holloway, 1982) of sex differences in the CC, no other subsequent study has actually evaluated the same 4 measurements, which include (1) the area of the CC, (2) the MSW, (3) the area of P5, and (4) subjective gender classification based on the shape of the splenium. de Lacoste-Utamsing and Holloway (1982) observed that the MSW was significantly greater in females, and each investigator correctly identified the gender of the CC of each subject, based on the shape of the CC. However, they did not describe their method of evaluating the shape of the splenium until a subsequent study (de Lacoste et al., 1986). Thus, only a few investigators made similar measurements (Bell and Variend, 1985; Holloway and de Lacoste, 1986; Demeter et al., 1988; Witelson, 1989), while others made different measurements (Weber and Weis, 1986; Oppenheim et al., 1987; Byne et al., 1988; Weis et al., 1988; Clarke et al., 1989). We observed that, though gender in our sample could not always be accurately determined from the CC, there was a significant association between the shape of the splenium and the gender of the subject. Furthermore, among our 27 absolute measures of the CC, only the MSW and P2 − P3 (C-L method; utilizing paired t test, but not Bonferroni adjustment for multiple comparisons) were sexually dimorphic. While other studies report that gender cannot be absolutely determined by the shape of the posterior CC (Weber and Weis, 1986; Byne et al., 1988; Weis et al., 1988), each study reporting subjective gender classification based on the shape of the splenium (Bell and Variend, 1985; Weber and Weis, 1986; Yoshii et al., 1986; Kertesz et al., 1987; Oppenheim et al., 1987) was able to identify correctly the gender in more than half of their subjects.

While some investigators have determined the regional areas of the CC by dividing it in a manner similar to the S-L method (Bell and Variend, 1985; Witelson, 1985; Weber and Weis, 1986; Oppenheim et al., 1987; Byne et al., 1988; Demeter et al., 1988; Clarke et al., 1989; Witelson et al., 1989), others have divided the CC in a manner similar to the C-L method (Nasrallah et al., 1986; Demeter et al., 1988; Clarke et al., 1989). However, it is important for investigators to measure the CC in a similar manner in order to compare results. In our data, P5, P4, and P3 adjusted for CC area are slightly larger in area in women than in men. Other investigators also have observed that the posterior components of the CC are slightly larger in females (de Lacoste-Utamsing and Holloway, 1982; Oppenheim et al., 1987; Byne et al., 1988; Weis et al., 1988), particularly when adjusted for CC area (Demeter et al., 1988; Clarke et al., 1989; $p < 0.05$). While several investigations report that the area of the CC is greater in females (de Lacoste-Utamsing and Holloway, 1982; de Lacoste et al., 1986; Holloway and de Lacoste, 1986; Byne et al., 1988), most studies report that it is greater in males (Nasrallah et al., 1986; Weber and Weis, 1986; Kertesz et al., 1987; Demeter et al., 1988; Weis et al., 1988); however, it tends to be greater in females when adjusted for sex differences in brain weight (de Lacoste-Utamsing and Holloway, 1982; Holloway and de Lacoste, 1986).

Although several studies report no significant decrease in CC area with aging, in our relatively larger group of adults, we did observe such a decrease with advancing age. Similarly, regions of the CC decreased significantly with age in both genders. Because neural atrophy does occur with aging, both the failure to age-match subjects and differences in age distribution may contribute to these conflicting results. We know of no other study that specifically age-matched its subjects; in fact, several did not mention the age of subjects (de Lacoste-Utamsing and Holloway, 1982; Oppenheim et al., 1987). In several studies, sex differences in the area of the CC appear to correspond to sex differences in the age of the male and female groups. Specifically, in an autopsy sample where the men were 19 yr younger than the women (Clarke et al., 1989; $p < 0.0001$), the CC of men were 15% larger than those of females. Likewise, in a group where females were an average of 10 yr younger than the males, the CC of females were 16% larger than those of males (Byne et al., 1988). The sex difference in the area of the CC appears to decrease when males and females are of similar ages. In a sample where the females were only 9 months younger than males, the CC of females were only 2% larger than those of males (Clarke et al., 1989). Similarly, in this study where the females were only 2.4 months younger than the males, the CC were only 1% larger in males. Thus, published results are difficult to interpret, with large age discrepancies and/or failure to report ages. Age-matching becomes even more significant in studies of fetuses (de Lacoste et al., 1986; Clarke et al., 1989) and children (Bell and Variend, 1985; Clarke et al., 1989), when significant age-related changes in the CC may occur over weeks or months (Witelson and Kigar, 1988).

Apart from differences in actual measurements of the CC and differences in age distribution, discrepancies in reports of CC sex differences may arise from relatively small sample sizes, differences in the general health of subjects, limited resolution of an MRI relative to a photograph of a postmortem section, and possible failure to obtain a precise midsagittal section of the CC. Furthermore, factors for which we were unable to account, such as genetic and racial constitution, handedness of the subject (Witelson, 1985, 1989; Nasrallah et al., 1986), and the environment (rats, Berrebi et al., 1988; Juraska and Kopcik, 1988) may influence the shape and size of the CC.

Further discrepancies in the literature may arise when multiple measurements of the CC are taken. With respect to this study, a number of evaluations of the shape of the CC, including subjective evaluation, MSW, and several bulbosity coefficients, consistently demonstrated a significantly more bulbous splenium in the CC of females; therefore, we feel confident that this difference exists. In contrast, a total of 23 measurements were made of areas of the CC and its subdivisions. We would expect by chance at the level of $p < 0.05$ that one of these areas would exhibit a sex difference. Indeed P2 − P3 was significantly larger in males. Similarly, Witelson (1989) exhibited a sex-by-handedness interaction in this region when the CC was examined by the S-L method, which originally motivated us to use this method in our study. However, following the conservative Bonferroni adjustment for multiple comparisons, we found no significant

sex difference in P2 − P3. Therefore, it is uncertain whether there are sex differences in the area of the P2 − P3 region, or whether the significance we obtained is a result of multiple comparisons. Interestingly, a larger P2 − P3 in males tends to make the splenium appear more bulbous in females.

When does sexual differentiation occur?

Although our sample size of children is small, it appears that sex differences in the shape of the CC may be present between the ages of 2 and 16 yr of age. The gender classification based on shape of the splenium was correctly identified in 1% more children than adults, and the percentage differences between bulbosity coefficients were greater between girls and boys than between women and men. However, neither the subjective gender classification nor the bulbosity coefficients reached statistical significance in children, perhaps because of the relatively small sample size. In contrast, the MSW was greater in boys than in girls, though it was greater in girls relative to CC area. However, a significantly greater MSW has been reported in female fetuses (de Lacoste et al., 1986).

How does sexual differentiation occur?

In the CC of the human being, it is not only unknown when sexual differentiation occurs, but also whether the process of sexual differentiation is due to genomic factors, the environment, and/or gonadal hormone levels. However, in laboratory animals, nearly all sexually dimorphic structures exhibit morphological differences during the perinatal period. Furthermore, structures that are sexually dimorphic in rats, including the cerebral cortex (Diamond, 1988) and the CC (Berrebi et al., 1988; Juraska and Kopcik, 1988), are influenced by environmental factors both pre- and postnatally in a sexually dimorphic manner. For example, the sexually dimorphic pattern of cerebral cortical asymmetry may be influenced by both prenatal stress (Fleming et al., 1986) and an "enriched" postnatal environment (Diamond, 1988), and the CC may be influenced prenatally by maternal alcohol consumption (Zimmerberg and Scalzi, 1989) and postnatally by handling (Berrebi et al., 1988). However, more striking have been data indicating that nearly all sexually dimorphic structures examined thus far have been shown to be influenced by perinatal gonadal hormone levels.

The mechanism by which environmental factors influence neural structure in a sex-dependent manner is unclear. In contrast, gonadal hormones may act, at least in some cases, during a critical period of perinatal developmental to influence the survival of neurons in sexually dimorphic nuclei (Nordeen et al., 1985). Because there is a concentration of sex steroids in the cerebral cortex of the developing rat (Sandhu et al., 1986) and rhesus monkey (MacLusky et al., 1986) and an elimination of neurons and their axons during the perinatal period (Berlucchi, 1981), it is conceivable that gonadal hormones influence the number of axons coursing through the CC of humans; such axonal elimination may explain sex differences in the CC of humans (Witelson, 1985; Clarke et al., 1989). In addition, gonadal hormones appear to influence myelination: in rats, estradiol increases myelination (Curry and Heim, 1966), and 5-*a*-reductase, the enzyme that converts testosterone to dihydrotestosterone, is present in high concentrations in white matter (Celotti et al., 1987), suggesting that testosterone may also be involved in this process.

Differences in myelination, number, or arrangement of axons?

It is unknown whether sex differences in regions of the CC correspond to sex differences in myelination, in the numbers of fibers, or to a different arrangement of axons coursing through the CC, perhaps caused by other sexually dimorphic neuroanatomical structures. Several studies indicate that there is no correlation between the number of axons coursing through the CC and the size of the CC. For example, in the splenium of rats, there are significantly more axons in females; however, there are more myelinated axons in males, resulting in a splenium that is not sexually dimorphic in terms of either area or MSW (Juraska and Kopcik, 1988). Similarly, in rhesus monkeys, there is approximately a 2-fold variation among animals between the density of axons and the midsagittal area of the CC, and there is no correlation between area of the CC and number of axons (LaMantia and Rakic, 1990).

Furthermore, the CC of children increase with advancing age: it is unlikely that this is caused by an increase in the number of callosal axons; rather, in the human there is protracted myelination of the CC after the first decade, and certain regions of the brain exhibit myelination throughout life (Yakovlev and Lecours, 1967).

Functional significance

Human males and females differ with respect to cerebral lateralization of neuropsychological function (for reviews, see McGlone, 1980; Beaton, 1985; Kimura 1987); furthermore, the midsagittal area of the CC may relate to cerebral specialization of function (Berrebi et al., 1988; Schmidt and Caparelli-Dàquer, 1989; Witelson, 1989). Some investigators propose that, in humans, the midsagittal area of the CC relates inversely to cerebral lateralization. For example, Witelson (1989) observed that regions of the CC that contain fibers connecting asymmetrical neural regions, such as the planum temporale (de Lacoste et al., 1985), were larger in individuals whose hand preference may indicate less cerebral specialization (Beaton, 1985). In contrast, in rats, greater lateralization may correspond to greater callosal size (Berrebi et al., 1988). In mice, the size of the CC directly relates to morphological asymmetry of the cerebral cortex: those animals with deficits in or the absence of a CC do not exhibit morphological cortical asymmetry, whereas animals with a normally developed CC do exhibit cerebral asymmetry (Schmidt and Caparelli-Dàquer, 1989). It is unknown whether sexually dimorphic neuroanatomical asymmetries, which occur in both rats (Diamond et al., 1983) and humans (Wada et al., 1975), underlie sex differences in functional asymmetry and/or correspond to the number of axons coursing through specific regions of the CC. However, if sexual dimorphism in the human CC is in fact related to a sex difference in the number or relative distribution of axons, then this difference may, in part, underlie sex differences in cerebral lateralization.

In contrast to structural sex differences in nuclei that are present in regions known to control reproductive function, such as the SDN-POA of the rat, whereby there are relatively dramatic sexual dimorphisms in terms of both structure and function, with generally little overlap between males and females, sex differences in regions not directly related to reproductive function, such as the CC in terms of structure and cerebral lateralization in terms of function, are relatively subtle, with considerable overlap between males and females. Compared to the sexually dimorphic nuclei, many of which appear to underlie

sexually dimorphic function, the significance of structural sex differences in regions not directly related to reproductive function is poorly understood.

Conclusion

The controversy regarding sex differences in the CC may subside with studies using consistent measurements of large samples of healthy, age-matched subjects. Utilizing several criteria, we observed that the *shape* of the splenium (considered here to be P5) was consistently wider or more "bulbous" in females than in males. In contrast, among 23 measurements of the *areas* of the CC and its subdivisions, only 1 division, P2 − P3 examined by the C-L method, exhibited a significant sex difference, which would be expected by chance. However, none of these differences reached statistical significance in children. After the establishment of sex differences within the CC, MRI may be useful in demonstrating a relationship between sex differences in neuroanatomy and neuropsychological function, and the role of gonadal hormones and the environment in the process of sexual differentiation.

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