

# Sex Differences in the Human Corpus Callosum: Myth or Reality?

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BISHOP, K. M. AND WAHLSTEN, D. *Sex differences in the human corpus callosum: myth or reality?* NEUROSCI BIOBEHAV REV 21(5) 581–601 1997.—It has been claimed that the human corpus callosum shows sex differences, and in particular that the splenium (the posterior portion) is larger in women than in men. Data collected before 1910 from cadavers indicate that, on average, males have larger brains than females and that the average size of their corpus callosum is larger. A meta-analysis of 49 studies published since 1980 reveals no significant sex difference in the size or shape of the splenium of the corpus callosum, whether or not an appropriate adjustment is made for brain size using analysis of covariance or linear regression. It is argued that a simple ratio of corpus callosum size to whole brain size is not an appropriate way to analyse the data and can create a false impression of a sex difference in the corpus callosum. The recent studies, most of which used magnetic resonance imaging (MRI), confirm the earlier findings of larger average brain size and overall corpus callosum size for males. The widespread belief that women have a larger splenium than men and consequently think differently is untenable. Causes of and means to avoid such a false impression in future research are discussed. © 1997 Elsevier Science Ltd.

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IF men and women think differently, their brains must also differ in some way. This holds true, even if the difference emanates largely from experience, because experience changes the brain (39,114). The size of cognitive gender differences has never been very large (58,69), and the difference has almost vanished for several abilities in more recently published reports (47,70). Of course, not all measures of behavior show small sex differences. For example, in the USA, boys possess considerably more knowledge about electronics, automobiles and machinery (58). Among 21 indicators of sexual behavior and sexuality, two (attitude towards casual intercourse and incidence of masturbation) exhibit male–female differences greater than 0.8 standard deviation (95), which is the conventional criterion for a large group difference in psychological research (27), although most (18 out of 21) show differences less than 0.5 standard deviation (SD). However, on tests of cognitive abilities, sex differences are usually small (58). In a review of 287 effect sizes for spatial visualization abilities (118), the average sex difference was 0.37 SD and only one kind of test (mental rotation) met the criterion for even a moderate effect size. For 254 effect sizes involving mathematical performance in 100 published studies, the male average exceeded the female average by only 0.2 SD, but for studies in which the samples were drawn from the general population, females scored slightly better than males (70). Given such small cognitive gender differences, it seems likely that only the most sensitive and refined

neurological techniques will be able to locate the relevant difference in brain tissue.

Neuroanatomists have scrutinized thousands of preserved brains in a search for meaningful variations that may somehow be related to differences in mental processes, a pursuit termed ‘cognitive neuroanatomy’ by Witelson (128). Overall size (100) or activity (54) of the brain is probably of little importance. Although the average brain size of men exceeds that of women by more than 100 g or 1 SD, average scores on intelligence tests are, by definition, equal (47), and the metabolic rate per unit volume of brain tissue is virtually the same (54). Large morphological differences are known in areas of the hypothalamus related to sexual behavior and reproduction (16,116), where the volume of the ‘sexually dimorphic’ nucleus of the preoptic area is 1.5 SD larger in males than females (64). However, major morphological sex differences in the cerebral cortex are not at all obvious. It is possible that functional activity of a region such as temporal cortex may be higher in one sex (54) without the area showing a morphological difference in histological sections. Furthermore, a morphological difference in one area of the brain may be related to overall brain size and may not reflect anything specific to the sex of the brain. When a sex difference in the size or shape of a part of the brain is identified, it is even more challenging to prove that it causes a gender difference in thinking and is not a mere correlate of the real action.

These difficulties notwithstanding, strong claims have

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been made about the importance for cognitive gender differences of one feature of the human brain, the corpus callosum, which contains millions of nerve fibers interconnecting the two cerebral hemispheres. In adults, the corpus callosum (CC) allows rapid transfer of information between the two halves of the cortex, and when it is cut surgically as a treatment for intractable epileptic seizures, the result is a 'split brain' where one hemisphere does not have access to important information from the other (113). It is conceivable that a difference in size of the CC might also have cognitive consequences, albeit lesser ones than complete surgical sectioning.

If the publicity that a finding receives from science writers in the popular media is any indicator, the sex difference in the corpus callosum is an established fact. A recent cover story in *Newsweek* magazine (14) stated that "In women, the back part of the callosum is bigger than in men. That may explain why women use both sides of their brain for language" (p. 51). A feature article in *Time* magazine (52) presented a brain diagram showing the corpus callosum highlighted with the caption: "Often wider in the brains of women than in those of men, it may allow for greater cross talk between the hemispheres—possibly the basis for woman's intuition" (p. 36). A feature article in *The Globe and Mail*, distributed nationally in Canada, announced that, after a long search, scientists had found "hard-core physiological evidence" of one difference: "Hot among the smoking guns is evidence that the corpus callosum...is larger and more developed in women" (3).

Academics, on the other hand, have become more circumspect. The second edition of the authoritative *Principles of Neural Science*, edited by Kandel and Schwartz, cited with approval a claim that the corpus callosum is 'sexually dimorphic' (75). However, in the third edition (74), the passage about the human corpus callosum was deleted with no explanation. Another leading text took note of several failures to replicate the finding and warned readers that "a sex difference is not yet established for the corpus callosum" (79).

Because of the stark contrast between current opinion in the popular media and among neuroscientists, as well as the continuing dispute in academic circles about the reality of the neural sex difference, we have gathered all available evidence on the topic for meta-analysis and reanalysed some previously published raw observations. Before presenting this material, we would like to explore briefly the history of the question in order to create a context for our conclusions and recommendations.

#### 1. A DISPUTE AT THE TURN OF THE CENTURY

Controversy is no stranger to the corpus callosum. In the 1905 issue of *Connecticut Magazine*, the anatomist Spitzka announced that the corpus callosum was substantially larger in ten brains from deceased men of eminence than in 'ordinary' men. The anatomist Bean (8) was especially impressed by the brain of Professor Joseph Leidy, himself a prominent morphologist who generously donated his body to his colleagues for study. The brain was fairly large (1545 g) but had a corpus callosum of record dimension (10.6 cm<sup>2</sup> in cross-section), prompting Bean to suggest that the "exceptional size of the corpus callosum may mean exceptional intellectual activity". When Bean discovered a brain of a

man of African ancestry having a corpus callosum of 9.1 cm<sup>2</sup>, larger than the mean of Spitzka's sample of eminents, he speculated that the otherwise unremarkable man may have been "an obscure genius".

Bean (8) himself located 152 brains from men and women of European and African ancestry, then searched for features of the corpus callosum typical of race and sex. His subjects were unclaimed bodies in the Baltimore area, people who ended their days in the City Alms House, the Bay View Pauper Asylum, a traffic accident or a hangman's noose. Bean's sample of brains had been preserved with nine different methods, ranging from suspension in a bucket of formalin to infusion through an artery of carbolic acid and alcohol, followed by shellac. After cutting each brain in half and drawing the outline of the corpus callosum, Bean plotted the area of the corpus callosum against brain weight and noted a strong positive relation. He perceived that people of African ancestry had a smaller front portion (genu) relative to the more posterior part (splenium) of the corpus callosum [see Fig. 1(A)], and he took this as a sign of deficient "self-control... and reason". He classified the corpus callosum according to shape and with considerable confidence attributed individual variations among those of African ancestry to their presumed tribal origins (Guinea Coast, Hottentot, Zulu) or to the extent of "white intermixture", which is quite a feat for a pathologist working without modern anthropological methods. He also delineated composite male and female 'types' of corpus callosum differing in shape.

Bean did most of his work in the Anatomical Laboratory at the Johns Hopkins University, whose director Franklin Mall was sceptical of many claims about brain and corpus callosum shape, having reviewed an extensive literature of the period. Mall (87) undertook his own study of 106 brains using an improved methodology, stating: "In order to exclude my own personal equation, which is an item of considerable importance in a study like this, all the tracings were made without my knowing the race or sex of the individuals from which the brains were taken." Plotting his results on a graph, he concluded "that there is no variation in either genu or splenium of the corpus callosum due to either race or sex" and that any group differences "are completely masked by the large number of marked individual variations". Mall dismissed several previous claims about group differences as "opinion supported by a strong personal prejudice" based on small samples or flawed methods.

Bean and Mall reached their opposing conclusions without the aid of formal statistical inference but they published their original observations, which allows reanalysis with improved techniques. It was well known years ago that men on average have larger bodies and brains than women, and it seems likely that a larger brain would exhibit a larger corpus callosum because most body parts tend to grow allometrically or proportionally to the whole (53). The most important question is whether any sex difference in the CC is simply a function of different brain sizes or instead there is a sex-specific effect. Confronted with colleagues who claimed they could determine a person's sex by examining the fixed brain, Mall (87) remarked: "I would like to ask them to separate a collection of 100 brains (50 of men and 50 of women) each of the same weight and see how well they can do it" (p. 6).

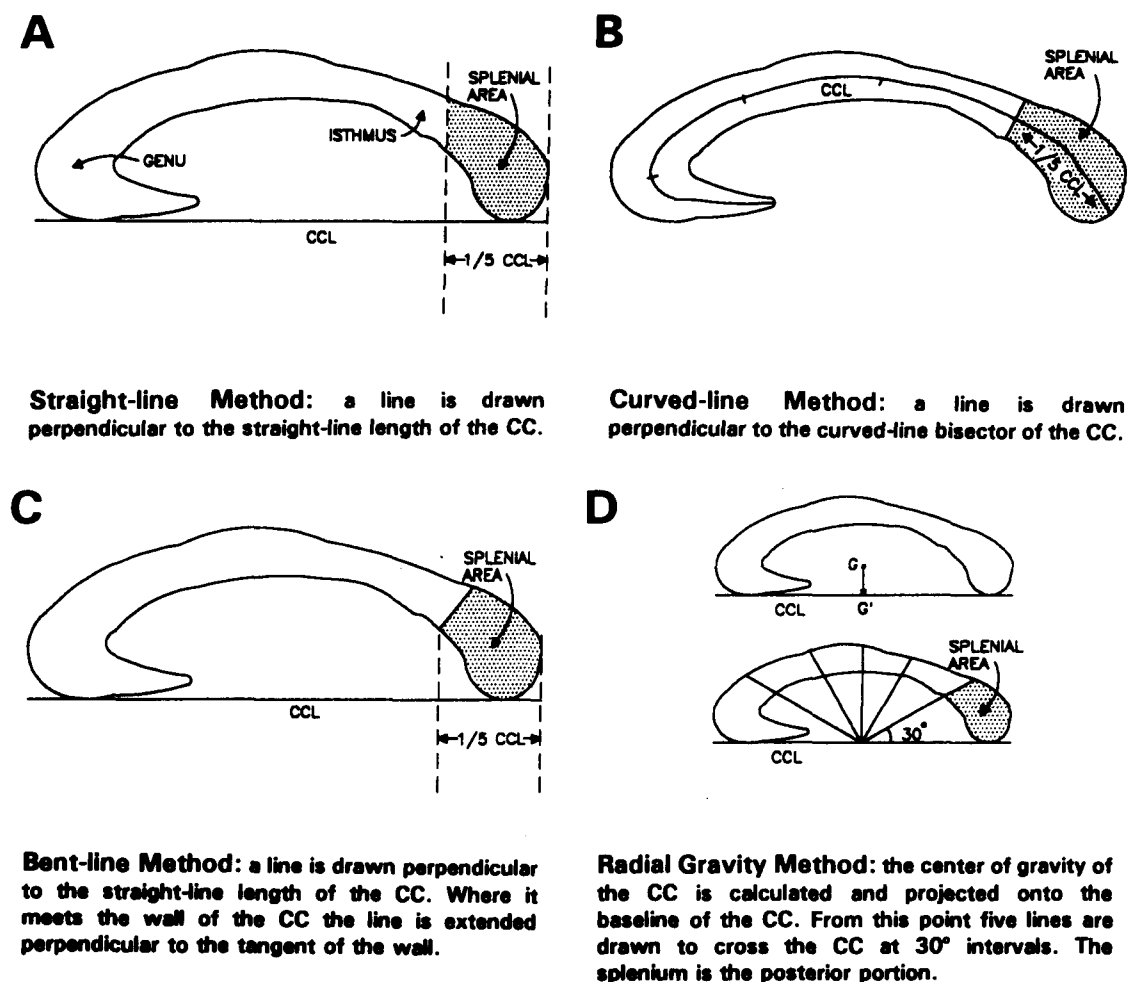


FIG. 1. Outlines of the corpus callosum at the middle of the brain showing the posterior portion (splenium), the adjacent isthmus, and the genu at the front end. The four panels (A, B, C, D) represent different methods of defining the splenium that were used in various studies listed in Table A1.

Today, we can equate brain size statistically with linear regression equations. The straight lines predicting corpus callosum area from brain weight are  $CC = 40.5 + 0.50 \times \text{BRAIN}$  for 123 values given by Bean (8) and  $CC = 251.2 + 0.26 \times \text{BRAIN}$  for 95 values from Mall (87), and these equations that take no account of ancestry or sex explain about 45% and 17% of the variability in CC size, respectively. Next, we ask whether the fit to the data improves significantly when 'dummy' variables are added

to the equations to represent ancestry and sex. As shown in Table 1, it does not. Hence, there is nothing at all about the size of the corpus callosum that is peculiar to any group of individuals in the two studies. Likewise, to assess whether the genu or splenium of the corpus callosum is relatively larger in any group, we should first predict the size of one part from the remainder of the corpus callosum, then introduce variables representing ancestry and sex to see if this added information improves the equations. For the data

TABLE 1  
SIZE OF EFFECTS IN A MULTIPLE REGRESSION EQUATION PREDICTING THE DEPENDENT MEASURE FROM GROUP VARIABLES AND A COVARIATE FOR DATA FROM BEAN (8) AND MALL (87)

Study	Measure	N	Ancestry	Sex	Covariate	Effect of covariate	Adjusted $R^2$
Bean	CC area	123	-0.085 NS	0.087 NS	Brain weight	0.698*	0.45
Mall	CC area	95	-0.029 NS	-0.084 NS	Brain weight	0.396*	0.17
Mall	Splenium	95	-0.013 NS	-0.077 NS	CC—splenium	0.474*	0.22
Mall	Genu	95	-0.062 NS	-0.066 NS	CC—genu	0.556*	0.32

Tabulated values are standardized regression coefficients or beta weights, which can vary from -1 to +1. When squared, these values will sum to  $R^2$  if the predictors are independent, which they are not in these data sets. The adjusted  $R^2$  is the unbiased estimate, not the raw multiple  $R^2$ . Significance levels (one-tailed): NS,  $p > 0.05$ ; \* $p < 0.001$ .

of Mall, it does not. (Bean did not report genu and splenium size for female brains.) The perception of Franklin Mall in 1909 was correct; individual differences within a group in corpus callosum size and shape overwhelm any trivial sex differences in the Baltimore samples, and no sex-specific difference in the CC is apparent. This is how matters stood shortly after the turn of the century.

## 2. IMPETUS FOR RENEWED DEBATE IN 1982

The modern history of the dispute dates from the widely publicized report in *Science* in 1982 of a new claim that the splenium of the corpus callosum shows "sexual dimorphism" (34). The initial findings were presented in a poster at the 1981 Society for Neuroscience meeting in Los Angeles (35). Data for 15 male and 13 female brains preserved in formalin were analysed, and the authors noted that the females had a significantly larger splenium area ( $p = 0.05$ ) and a "visually obvious" more bulbous splenium. The 1982 *Science* article, which was submitted for publication before the Los Angeles meeting, claimed to be the first report of a reliable sex difference in human brain morphology and argued for relevance to cognitive gender differences. Inexplicably, the report described only 14 (nine male and five female) of the original sample of 28 brains. Whereas the overall area of the corpus callosum was almost identical for men ( $704.3 \text{ mm}^2$ ) and women ( $708.3 \text{ mm}^2$ ), the average size of the splenium (defined as posterior fifth) of the corpus callosum was larger in women ( $218.3 \text{ mm}^2$ ) than men ( $186.1 \text{ mm}^2$ ). The latter difference yields  $t = -1.85$  which has a two-tailed probability of  $p = 0.0895$ . A reasonable criterion for statistical significance in a study that analysed five measures of each corpus callosum is Type I error probability  $\alpha = 0.05/5 = 0.01$  (a slightly conservative standard when the tests are inter-correlated). We conclude that the results presented in the 1982 report do not come close to demonstrating that females have a significantly larger posterior fifth of the corpus callosum. Only the width of the splenium met an adequate criterion. Because this mere difference in shape does not even imply a difference in the number of nerve fibers in the splenium, there is no reason at all to speculate about possible functional consequences. The 1982 article simply did not meet conventional scientific standards for demonstrating a sex difference in the size of the splenium.

Nevertheless, the *Science* article reached an audience beyond the fringes of the scientific community and even caught the attention of talk show host Phil Donahue, who credited de Lacoste-Utamsing and Holloway with finding that females had a corpus callosum "as much as 40 percent larger" because of "an extra bundle of neurons that was missing in male brains". Donahue proposed that this may be the basis for "women's intuition" and that men may have an advantage because "communication between their hemispheres is slow" (41). As recently as 1991, the 1982 study was being cited in popular science writing as the authority that "precisely discerned" women have a larger "message-exchange centre" (88).

Among scientists, the annual meeting of the Society for Neuroscience became the venue for hearings on this matter. In the same year the *Science* article appeared, a follow-up study by the Dallas group ((7), later appeared as (32)) claimed that the sex difference also occurs in human fetuses

and hence is "mediated by hormonal or genetic factors". However, in the next year, Witelson (124) reported no sex difference in the absolute size of the corpus callosum or any subdivision in formalin-fixed brains of cancer victims, although the female splenium was slightly larger relative to brain weight. After a 1-year hiatus, the dispute intensified in 1985 when three groups reported a failure to confirm the de Lacoste-Utamsing and Holloway (34) claims (13,36,92). Whereas Witelson's work was part of an ongoing study of lateralization of function, certain of the 1985 contributions and several subsequent studies were instigated by the 1982 *Science* article. Other investigators examined the corpus callosum because of a possible relevance to mental disorder or neurological disease, and gradually a large amount of information on the putative sex difference accumulated.

## 3. META-ANALYSIS POINTS TO NO DIFFERENCE

### 3.1. Selection of studies

A comprehensive literature search found 49 independent studies that examined sex differences in the CC dating from 1982 to 1994. The search was initiated by conducting computer searches of the literature (MEDLINE, PsycINFO, and Current Contents) using 'corpus callosum' and 'sex differences' as the search terms. Studies not listed on the computer databases were identified through the bibliographies of papers located in the original searches. The world literature contains more than 49 studies but several repeat data for the same subjects. For example, Witelson (125) reported a sample of 42 brains, and these were later included in an article involving 50 brains (126), and a letter including 62 brains (127) and few measurements, so we used only the large 1989 study in the present review. Weis et al. (122) presented virtually the same results in another article (123), so we considered only the first publication. The poster by Baack et al. (7) was apparently expanded to a full journal article with Baack's name deleted and Holloway's added (32), so we used the full report. Denenberg et al. (38) used the raw data from Kertesz et al. (76) but both are included in the set of 49 studies because their measures were sufficiently different, although we never utilized both sources when assessing a single measure of the CC. Cowell et al. (30) also analysed this data set, but because no novel measurements were made, it is not included in our analysis. Cowell et al. (28) and (29) were also excluded because they use the same raw data as Allen et al. (4). Clarke et al. (25) and Prokop et al. (102) were each treated as two separate studies because two different methods were used to examine two different groups of subjects in each study. Holloway et al. (66) was treated as three separate studies because three different samples of subjects were examined.

### 3.2. Methods utilized in studies

The 49 studies employed a variety of subjects, methods and measurement parameters (see Table A1 for a full summary). In the following paragraphs, each study is always referenced by its reference number (1, 2, etc.) and is also referenced by its number (Tables A1 and A2) (A1, A2, etc.) when material in the appendices is being discussed. Sixteen studies examined brains of the dead with histological techniques, and 33 used Magnetic Resonance Imaging (MRI) to

TABLE 2  
RESULTS OF META-ANALYSIS OF SEX DIFFERENCES IN THE BRAIN

Measure	Number of studies	$d_+$	95% CI		$Q$	$p$ for $Q$	$n$ for 80% power
			Lower	Upper			
Brain weight	8	1.20	0.95	1.46	17.2	0.02	13
CC area	41	0.21	0.13	0.29	59.2	0.03	360
Splenium area	23	0.04	- 0.08	0.16	24.5	0.32	9872
Splenium/CC ratio	17	- 0.11	- 0.25	0.02	54.7	0.000001	1307
Splenium width	28	- 0.25	- 0.35	- 0.15	160.0	$7.7 \times 10^{-21}$	255
Splenium width†	23	- 0.04	- 0.15	0.06	17.4	0.74	9872
Isthmus area	7	0.12	- 0.06	0.30	10.8	0.09	1099

Includes only those studies (\*) that provided sufficient statistical details to determine an effect size ( $d$ ) for the sex difference. If the 95% confidence interval (CI) for the combined estimate  $d_+$  does not include zero, then it is reasonable to conclude that the best estimate of effect size is significantly greater or less than zero. The  $p$  value for the  $Q$  test of homogeneity is the probability that the studies were sampled from populations having the same effect size. Sample sizes per group to achieve power of 80% when  $\alpha = 0.05$ , two-tailed, were determined using the method of Wahlsten (119).

†Not including five studies by de Lacoste or Holloway where  $d < - 0.89$ .

visualize the midsagittal region of living brains. Although the resolution of the image obtained with MRI is lower than with post-mortem techniques, MRI involves less distortion of the brain and allows psychological testing for convenient assessment of brain-behavior correlation. In the post-mortem studies, most of the subjects had died from disease processes which, along with any medical treatment, may have changed morphological brain structure. Several MRI studies used neurologically normal subjects, but others examined patients with schizophrenia (A5, A19, A29, A42, A49; (91,56,104, 130,105)), Alzheimer's disease (A7; (132)), AIDS (A40; (82)), multiple sclerosis (A10, A40; (111,82)), unipolar depression (A43; (131)), bipolar affective disorder (A19; (56)) or gender dysphoria (A33; (45)). For these studies, all of which reported data separately for neurologically normal comparison groups, our review of sex differences included only the normal groups. One study, reporting combined data for normal controls and epileptics, was included because there were no significant effects attributable to clinical diagnosis (A13; (94)). Most studies reported similar mean ages for their male and female samples, but only Allen et al. (A30; (4)) actually age-matched subjects. We analysed data from only adult subjects, except for Bell and Variend (A2; (9)) who examined children, and Allen et al. (A30; (4)) where combined data from adults and children were included. The handedness of the subjects was not reported or examined in the majority of these studies, although a few included equal numbers of right- and left-handed subjects within each sex or used only right-handed individuals. Judging from the complete lack or very sketchy descriptions of how subjects were chosen for inclusion, it is unlikely that any of these studies involved unbiased samples of the male and female populations. However, sources of male and female subjects as well as measurement methods within a study appeared to be very similar, and there is no reason to believe that the sex difference itself was markedly biased. Despite the diversity of details across studies, they provide good subjects for meta-analysis because they measured the same things: brain size, the corpus callosum and its components. For all variables where sufficient details were published to compute effect size (see data in Table A2), we performed a meta-analysis of sex differences (59,68). A method has been devised recently for incorporating a study into a larger meta-analysis when an effect size cannot be

estimated from the information given (19). Our method of omitting such studies from the meta-analysis of a specific measure tends to bias results towards a larger effect size because studies reporting non-significant differences tend to be those with a dearth of details. In view of the small effect sizes found with our simpler approach (Table 2), we did not recompute the results using the new methodology. The data on fetuses from de Lacoste et al. (A3; (32)) were not included in the meta-analysis of studies reporting values from children or adults. The two-tailed probability values for the sex differences in Table A2 were calculated by us whenever means and standard deviations were available, because in a surprising number of cases (25%), the published probabilities were incorrect. There was no evidence of any significant difference between the published and calculated probabilities ( $p = 0.80$ ).

### 3.3. Other review papers

Several summaries or reviews of sex differences in the human corpus callosum have been published. Articles by Witelson (126) and Clarke et al. (25) contain summary tables and brief reviews of studies of sex differences in the corpus callosum, although no attempt is made to integrate the results statistically, and few studies are examined (less than 15). Holloway et al. (66) include an appendix in which 15 studies are described and their similarity to Holloway et al.'s is commented upon. Byne (21) and Fausto-Sterling (46) review 18 and 17 recent studies, respectively, and reach conclusions similar to ours, which are based on more studies and a formal meta-analysis. A meta-analysis of corpus callosum size and schizophrenia by Woodruff et al. (129) concludes that there was a significant reduction in corpus callosum area in schizophrenics compared with normal controls. A meta-analysis of sex, age and handedness differences in the corpus callosum has been conducted by Driesen and Raz (43). Based on 36 studies that examined the sex difference in CC area and 21 that examined the difference in splenial area, they conclude that absolute corpus callosum and splenial areas are larger in men than in women, and CC area adjusted for brain size is larger in women. Our meta-analysis includes a greater number of studies, an evaluation of the reported sex difference in splenial width, and a more complete examination of relative

corpus callosum measurements. An earlier version of our meta-analysis reviewed 33 studies and has been presented previously (120).

### 3.4. Brain weight

The 13 studies that analysed whole brain size confirmed the established fact of a larger male average. Only one study of a small sample of elderly cadavers (A4; (67)), one of fetuses (A3; (32)), one of children (A2; (9)), and another examining mid-sagittal brain area (A43; (131)) failed to detect a sex difference significant at  $\alpha = 0.05$ . Eight reports of adult brain weight published adequate details to allow a combined estimate of the statistical size of the sex difference. If  $\sigma$  is the standard deviation of scores within a sex, and  $\mu_1$  and  $\mu_2$  are the true means for males and females in a large population, then  $\delta = (\mu_1 - \mu_2)/\sigma$  is the true effect size in terms of standard deviation units. Cohen (27) regards effect sizes of 0.2, 0.5 and 0.8 to be small, medium and large, respectively. The unbiased estimate of  $\delta$  is the coefficient  $d$  calculated according to formula 5.10 in Hedges and Olkin (59). Except for the results from Holloway and de Lacoste (A4; (67)), the sex differences were large ( $d > 0.75$ ) in the other seven studies, and four of these exceeded  $d > 1.0$  (see Table A2). The discrepancy between studies could occur merely from sampling error because so few cadavers were polled in the one study. A combined estimate of  $\delta$ , termed  $d_+$ , can be derived by a procedure that gives more weight to studies with larger samples and/or smaller variances within a sex ((59), formula 6.6). The  $Q$  statistic can also be calculated ((59), formula 6.25) to test whether the estimates of  $d$  differ significantly between studies or are reasonably homogeneous. For large samples,  $Q$  tends to be distributed as  $\chi^2$ . As indicated in Table 2, for brain weight the combined estimate of the sex difference is  $d_+ = 1.20$  and the studies are reasonably homogeneous ( $p = 0.02$ ). Because the 95% confidence interval of this  $d_+$  value does not include zero, it follows that the male average brain size is significantly greater than the female average. This result is in good agreement with the findings of Ho et al. (61), which yield  $d = 1.10$  for a large sample of 811 brains of European ancestry as well as data from Bean (8) whose comparable numbers yield  $d = 1.32$ . Effect size  $\delta$  is related to  $\omega^2$ , the proportion of total variance attributable to the group difference, by the formula  $\omega^2 = \delta^2/(\delta^2 + 4)$ , which indicates that a true  $\delta = 1.20$  is equivalent to  $\omega^2 = 0.26$ . Even this very substantial sex difference implies that a large majority of variation in brain size resides within a group having the same sex. Nevertheless, the sex difference in whole brain size is very large in statistical terms, as judged by the kinds of effects commonly studied by psychologists.

### 3.5. Corpus callosum size

#### 3.5.1. Absolute corpus callosum size

A total of 47 of the 49 studies evaluated the sex difference in CC area (Table A2) and five (A5, A10, A17, A23, A49; (91,111,25,126,105)) found an effect significant at  $\alpha = 0.05$  (two-tailed), all with a larger male average, as is expected from simple allometry. However, several others found positive  $d$  values short of significance. As urged by Schmidt (108), meta-analysis of the larger body of evidence provides

a far superior estimate. In this case, the combined  $d_+ = 0.21$  significantly exceeds zero and the results of the 41 studies with adequate details are reasonably homogeneous (Table 2). There can be little doubt that, on average, CC area is larger for adult males, as originally reported by Bean (8) and Mall (87). It is also apparent that the size of the sex difference, although real, is rather modest, accounting for only 1.0% of total variance in human CC size.

Because measures of CC area in the various studies were intended to represent the same structure, it was meaningful to perform an analysis of variance using group means and standard deviations given in Table A2. In this analysis, the studies variable was treated as a fixed effect because an effort was made to include all studies in the data set. This exercise indicated very large differences among studies ( $F = 15.4$ ,  $df = 40/2348$ ,  $p < 0.00001$ ) and a slightly larger CC for males ( $F = 7.9$ ,  $p = 0.005$ ). The differences among studies are significant if the studies variable is treated as a random effect ( $F = 8.8$ ,  $df = 40/40$ ,  $p < 0.0005$ ). Considering only the 14 post-mortem studies, males had a larger weighted mean CC area ( $647.3 \text{ mm}^2$ ) than females ( $632.4 \text{ mm}^2$ ), but the difference was not significant. Instead, there was a study by sex interaction ( $F = 2.1$ ,  $df = 13/510$ ,  $p = 0.01$ ) that occurred because five studies by de Lacoste, Holloway and co-workers (A1, A4, A24, A27, A39; (34,67,31,65,66)) found the female CC area to be larger than male, contrary to the other nine post-mortem studies. For the 27 MRI studies, the sex difference was significant (males =  $646.4 \text{ mm}^2$ , females =  $620.6 \text{ mm}^2$ ,  $p = 0.0006$ ), but the study by sex interaction was not ( $p = 0.20$ ). The difference in mean CC area among MRI studies was rather large ( $F = 23.7$ ,  $df = 26/1837$ ,  $p < 0.00001$ ,  $\text{est } \omega^2 = 0.24$ ). The mean CC areas from the MRI and post-mortem methods were comparable. Despite the immense variation in CC size among studies, there was only a modest heterogeneity in the magnitude of the sex difference.

#### 3.5.2. Relative corpus callosum size

The larger average CC size for males could reflect a mild allometric relation with brain size, which is substantially larger in males ( $d_+ = 1.2$ ), or there might be a sex effect on CC size relative to brain size. Four studies (A12, A35, A37/38; (2,35,37,66)) reported correlations between CC area and whole brain weight separately for males and females. These eight correlations yield a combined estimate ((59), p. 231) of  $r = 0.29$ , significantly above zero, with a 95% confidence interval from 0.15 to 0.42. This value is far below the correlation of more than 0.6 calculated from the data of Bean (8) that almost certainly was inflated by the radically different methods of brain fixation in his diverse sample. For a more homogeneous sample of brains fixed soon after death with 10% formalin, the correlation of CC size with brain size is modest but clearly not zero. If the sex difference in CC size can be accounted for entirely from variation in overall brain size, then the approximate effect size for CC area expected purely from an allometric relation should be the product of the sex effect size for brain weight and the correlation between brain weight and CC area. This yields an expected effect size for CC area of  $1.20(0.29) = 0.35$ , but the true CC size difference could be considerably above or below this value because it is based on sample values. The lower limit of the 95% confidence interval for brain size (Table 2) is  $d_+ = 0.95$  and the lower limit for the

CC vs. brain size correlation is  $r = 0.15$ , so a value for the CC size difference of  $0.95(0.15) = 0.14$  would not be unreasonable. This value is a little below the  $d_+ = 0.21$  observed for CC area. Hence, the available data provide no solid grounds for a belief in a sex-specific effect on CC area. Because  $d_+ = 0.21$  is somewhat below the expected value of 0.35, the possibility remains that there may be a very slight tendency for the female CC to be greater than expected purely from allometry.

The CC connects neurons only in the cerebral cortex, so any correlation with whole brain size is not expected to be large. Indeed, Witelson (A23; (126)) observed a higher correlation ( $r = 0.48$ ) between cerebral cortex weight and CC area. Cortex volume or weight would certainly be a better measure than brain weight for assessing allometric growth of the CC, although considerably more labor and anatomical knowledge are required to obtain it. Cortical volume can also be estimated if a series of sections through the brain is taken with the MRI procedure ((5), A44; (18)), which will be much more costly. When only the midsagittal section is available, the area of the cerebrum in this plane can be computed and compared with the area of the CC. This measure of cerebrum size is sensitive to the shape of the brain and is less satisfactory than a volume measure that is proportional to the number of neurons in the entire cortex. For this reason, failure to find a significant correlation between midsagittal cerebrum area and CC area with the MRI method (A8, A45; (26,76), see also (99)) does not convince us that the CC shows no allometric relation with brain volume. The allometric relation is rather weak and will not be detected with insensitive measures.

About half of the 49 studies of CC size examined the relation with brain size in some manner. Although none employed the multiple regression method that we propose for the data of Bean and Mall, seven used analysis of covariance in almost the same way, and six found no sex differences in CC size when brain or cortex size was used as a covariate (A2, A23, A37/38/39, A42, A44, A46; (9, 126,66,130,18,63)). Only Holloway et al. (A27; (65)) found any significant sex difference when cortical area was used as a covariate (female > male;  $p = 0.018$ ). Habib et al. (A34; (55)) took account of brain size with the MRI method by magnifying each midsagittal scan so that the length of the brain was 170 mm, and resulting CC measures revealed no sex differences. This seemingly elegant approach entails a peril, however. Suppose male brain size is substantially larger but the sexes have the same absolute CC size. Magnification to equate brain size will generate a larger CC for females. Whether or not this is appropriate depends on whether CC size and brain size are strongly correlated in the data. If the observed correlation is near zero, there is no reason to adjust one measure for the influence of another because there apparently is no such influence. Otherwise, the consequences would be the artificial creation of a sex difference that could mislead the unwary. Hence, regression or covariance methods that take into account the actual strength of the correlation are far superior.

Biologists have discussed various ways to express the size of a part ( $Y$ ) as a function of the whole ( $X$ ) and found little to recommend a simple ratio. When the relation of  $Y$  to  $X$  is allometric (53), an exponential function  $Y = aX^b$  can account for many kinds of relations. The coefficient of

allometry ( $b$ ) is generally estimated from the data because so many departures from purely geometric or physiological expectations are known (109). The linear equation  $Y = a + bX$  frequently accounts for the data just as well as  $Y = aX^b$  (112), and the use of log transformations is not always necessary prior to the regression analysis. An allometric or linear regression equation is usually very effective in removing the influence of overall size ( $X$ ) from a data set (e.g. (107)), but the ratio  $Y/X$  tends to be artifactually correlated with size  $X$  and have pronounced skew (6). Results of experiments or group comparisons may be quite misleading when a ratio is employed to adjust for the influences of overall size (40,97).

In some circumstances, a ratio may be appropriate because it is easily interpreted. For example, the ratio of splenium area (posterior fifth of the CC—see Fig. 1 and the following section) to total CC area is an indicator of shape or bulbosity of the CC. The greater this percentage, the larger is the splenium in relation to the more anterior structures. A ratio of CC area to brain volume or weight, on the other hand, has no clear anatomical meaning, and for these variables, a regression analysis is preferable. Using the  $2/3$  power of brain weight rather than brain weight itself when forming a ratio (e.g. A37/38/39; (66)) does not address the shortcomings of ratio measures. The objective of this procedure is to convert brain weight, a volume measure in three dimensions, to the same scale as cross-sectional area of the CC that has only two dimensions. At the same time, one can argue cogently that no scale transformation is required because a neuron that exists in three dimensions sends an axon through the CC that is then measured appropriately in two dimensions; hence, the more neurons that send axons through the CC, the larger should be the midsagittal CC area. It is well known that many regions of the adult cerebral cortex do not send axons through the CC, and it is possible for one individual to have more CC axons, even though the cortical zone of origin is not enlarged (e.g. (80)). Consequently, the proper constant of proportionality for comparing CC area with brain weight should be estimated from the data.

Nevertheless, the most common approach was to use the ratio of CC size to a measure of whole brain size, either brain or cerebrum weight of the dead or midsagittal brain or cerebrum area of the living visualized with MRI. Ten of these (A5, A14, A19, A29, A33, A35, A38, A43, A48, A49; (92,106,56,104,45,2,66,131,101,105)) found no sex difference in the ratio, whereas eight found females to have a significantly higher ratio (A4, A8, A15, A24, A25, A27, A37, A39; (67,76,117,31,44,65,66)). In some instances, a sex difference that was apparent with a ratio measure was not significant when analysis of covariance was used with the same data (e.g. A37/38/39; (66), for CC area/brain weight<sup>2/3</sup>). Several studies reported the correlation between CC area and brain size, but no study examined the crucial correlation between brain size and the ratio measure itself. For the data of Mall, we found a correlation of  $r = -0.314$  between brain weight and the CC area/brain weight ratio, indicating that the ratio did not fully adjust for the relation with brain size, whereas our multiple regression procedure performed this adjustment in a manner that completely removed the linear relation of brain weight and CC area from the CC data within a group. Furthermore, using a CC/brain size ratio for the data from Bean created a



significant effect of ancestry ( $p < 0.001$ ) when regression analysis revealed no such effect (see Table 1). Considering all of the above statistics and arguments, we conclude that there is no evidence of a sex-specific effect on overall size of the CC. Unadjusted CC size is slightly larger in males. Appropriate statistical adjustment for brain size generally results in no sex difference.

### 3.6. Splenial size

#### 3.6.1. Anatomical definition of splenial area

De Lacoste-Utamsing and Holloway (A1; (34)) originally pointed to the splenium of the CC as the site of an alleged sex difference, and several subsequent studies also looked here. The definition of the splenium turns out to be rather arbitrary. There is no anatomical landmark visible in stained brain tissue or an MRI scan that demarcates this region. The 'splenium' does not correspond to a group of axons from a specific region of cerebral cortex; instead, axons from visual cortex, for example, occupy several regions of the CC, although they are more concentrated in the splenium (85). The splenium was most often defined as the posterior fifth portion of the corpus callosum (see Fig. 1), but seven studies defined it as the posterior fourth, one defined it as the posterior tenth, and five did not report how they defined this region (see Table A1). Okamoto et al. (A28; (93)) defined it as the posterior third portion, which actually is splenium and isthmus, and therefore was not included in the analysis of splenial area. Most studies reported splenial area in absolute terms, but five (A9, A14, A19, A21, A22; (96,106,56,102)) reported only the percentage of callosal area in the splenium, Kertesz et al. (A8; (76)) reported the percentage of the brains where the splenium was larger than

the genu by visual examination, and Habib et al. (A34; (55)) reported splenial area after magnifying to a standard brain size. The various studies also differed in the methods used to delineate the splenium (Fig. 1). Twenty-one studies used the straight-line method, two used the curved-line method, five used the bent-line method, and three used the radial gravity method. Denenberg et al. (A31; (38)) used a unique method in which factor analysis was conducted on 99 equally spaced callosal widths and widths 89–94 and 95–99 were taken by us to be the splenium. Elster et al. (A25; (44)) used visual inspection for 80% of their subjects and ten other studies did not report the method used.

#### 3.6.2. Absolute splenial size

For the studies that reported splenium area in square millimeters, the sex effect is expressed in Fig. 2 as the absolute difference between the number of square millimeters for males and females. The large variation in differences between studies is noticeable and only the study by de Lacoste-Utamsing and Holloway (A1; (34)) exhibits a difference much removed from zero. Among the 28 studies of splenial area, none found any sex difference significant at  $\alpha = 0.05$ . For the 23 studies providing sufficient details, the combined  $d_+ = 0.04$  did not differ significantly from zero. Because the sex differences were so small in almost every study, it is unlikely that the precise method of defining the splenium was very important. Indeed, comparisons of partitioning methods were conducted in several studies (A12, A17/18, A30, A42, A45; (37,25,4,130,26)) and none observed any sex related bias.

#### 3.6.3. Relative splenial size

When splenium area was assessed with total CC area or brain or cerebrum weight as a covariate, most studies found

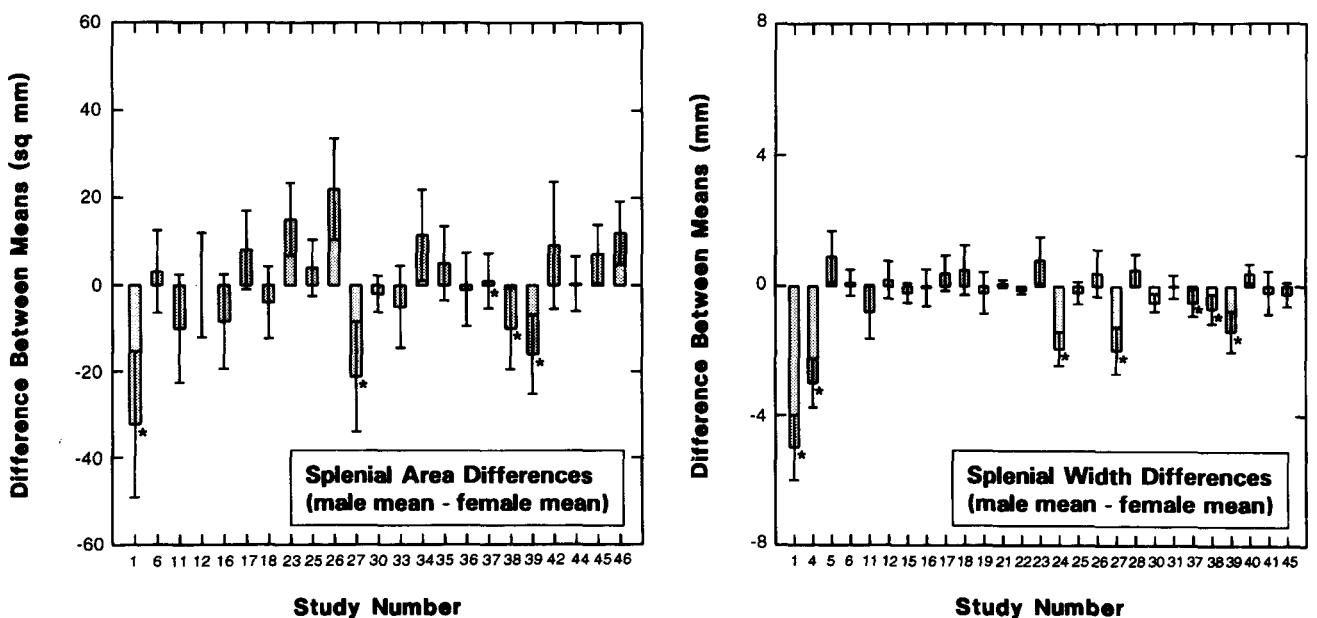


FIG. 2. Differences between mean values of males and females for measures of the splenium of the corpus callosum observed in several studies used in the meta-analysis. Study number corresponds to information given in Table A2. A positive difference indicates that the male mean is larger. Standard errors of the difference between means are shown by brackets. Asterisks (\*) indicate studies conducted by de Lacoste or Holloway and coworkers. (A) Cross-sectional area of the splenium reveals that only studies A1, A27 and A39 (34,65,66) found any substantial difference in favor of females, although they were not significantly less than zero. (B) Maximum width of the splenium reveals that studies by de Lacoste or Holloway and co-workers (A1, A4, A24, A27, A39; (34,67,31,65,66)) were the only ones to observe a significantly wider value for females.



no significant sex difference (A2, A6, A17, A23; (9,121,25,126)). Only Holloway et al. (A37/38/39; (66)) found larger splenia in females when assessed with brain weight as a covariate ( $p = 0.0074$ ). For relative splenium size, a ratio is a very good indicator because the numerator and denominator have the same scale of measurement, and the ratio itself has a straightforward interpretation. If the ratio is higher in females, their splenium is more bulbous. The ratio of splenium area to total CC area resulted in 13 studies reporting no sex difference significant at  $\alpha = 0.05$  (A9, A11, A18, A21, A22, A23, A25, A27, A30, A35, A36, A39, A45; (96,22,25,102,126,44,65,4,2,115,66,26)), two finding males exceeding females (study A19, (56),  $p = 0.0008$ ; study A26, (50),  $p = 0.0261$ ), and four finding females larger (study A14, (106),  $p = 0.02$ ; study A17, (25),  $p = 0.02$ ; study A37, (66),  $p = 0.03$ ; study A38, (66),  $p = 0.04$ ). Two studies also reported that the ratio of the genu to the splenium was higher in females (study A19, (56),  $p < 0.002$ ; study A43, (131),  $p = 0.05$ ). Meta-analysis of the splenium area/CC area ratio (Table 2) indicated that the combined estimate of the sex difference ( $d_+ = -0.11$ ) was not significantly different from zero. Thus, even when judged relative to brain or total callosal size, the area of the splenium reveals no convincing evidence of a sex difference. From this analysis, it is clear that, rather than there being a sex difference in splenial size as reported in the media, males and females have very similar absolute and relative splenial areas.

### 3.7. Splenial width and shape

The only sex difference in the de Lacoste-Utamsing and Holloway (A1; (34)) report that was significant by conventional criteria was a greater thickness or width of the splenium for females, resulting in what appeared to the eye to be a more 'bulbous' posterior of the CC. Accordingly, several studies attempted to replicate this finding. Most defined splenial width to be the maximum width within the splenium taken perpendicular to the outline of the callosum, but others defined it as the maximum horizontal or vertical diameter (A6, A9, A16, A21, A22; (121,96,122,102)), the width of the line dividing the posterior fourth region from the rest of the callosum (A5, A19, A29, A42, A43; (91,56,104,130,131)), the posterior fifth dividing line (A13; (94)), or the largest of 10 evenly spaced thicknesses within the splenium (A17, A18; (25)). For the Denenberg et al. (A31; (38)) analysis, we calculated splenial width to be the mean for widths 89–94 and 95–99, which were identified as separate factors with factor analysis. Oppenheim et al. (A9; (96)) reported splenial width as a percentage of callosal length, whereas the others reported absolute width. With so many definitions of splenial width, the question arises as to whether this would substantially influence the size of the sex difference. It is noteworthy that Weber and Weis (A6; (121)) obtained the same results for three different definitions applied to their data, and Weis et al. (A16; (122)) found that 10 different measures of width also led to the same conclusions.

Of the 33 studies that analysed sex differences in splenial width, seven found significance at  $\alpha = 0.05$ , six of these being studies with a larger female mean width (A1, A3, A4, A24, A27, A39; (34,32,67,31,65,66)) and one (study A2; (9)) reporting a larger male mean width. Analysis of the 28

studies that provided adequate information resulted in a combined  $d_+ = -0.25$  that was significantly different from zero. However, the test of homogeneity indicated that the estimated effect sizes did not come from the same population ( $p = 7.7 \times 10^{-21}$ ). Alarmed at this extremely small probability, we scrutinized the data and discovered that only five studies by de Lacoste, Holloway and co-workers obtained large effect sizes. Omitting these five (A1, A4, A24, A27, A39; (34,67,31,65,66)) produced a homogeneous population of estimated  $d$  values and a combined  $d_+ = -0.04$  (see Table 2 and Fig. 2). The discrepancy in results with and without the five studies by de Lacoste, Holloway and co-workers is perplexing, and we could find no methodological reason for it. Their report on fetuses (A3; (32)) also indicated a wider splenium in females. It is quite extraordinary that these six studies by de Lacoste, Holloway and co-workers invariably found an effect size of  $-0.89$  or even more negative, whereas the most extreme effect size in favor of females among the other 22 studies was  $-0.46$  (A38; (66)). It is especially difficult to understand this glaring discrepancy because the 1982 Science article claimed the area of the splenium was also much larger in females ( $d = -0.96$ ), but the three subsequent articles involving de Lacoste did not report splenial area.

If the splenium of females is truly more bulbous, then of course splenial area relative to total CC area should also be greater for females, which it is not (Table 2). Several investigators applied some more elaborate index of bulbosity or circularity. Allen et al. (A30; (4)) cited a "striking sex difference" with females being more bulbous, but the difference was significant at only  $p = 0.038$ , which, to us, is not so striking. One other group also found females to be more bulbous (A17, (25),  $p = 0.003$ ), one found males to be more circular (A6, (121),  $p = 0.05$ ), one found consistent right-handed females to be the least bulbous (A34, (55),  $p = 0.01$ ), and three found no difference (A11, A18, A26; (22,25,50)). De Lacoste-Utamsing and Holloway (A1; (34)) emphasized that the greater female bulbosity was visually obvious. Consequently, eight studies assessed the ability of human observers to sort outlines of the CC into two piles according to sex. Six found no significant association between actual and judged sex (A2, A8, A9, A12, A17/18, A33; (9,76,96,37,25,45)), whereas two found bulbosity to be predictive of sex (A7, (132),  $p = 0.025$ ; A30, (4),  $p = 0.001$ ). In addition, Ferrario et al. (48) used the more sophisticated elliptic Fourier analysis to compare the shapes of male and female corpus callosa and found no significant difference.

Altogether, the 44 studies that searched for some kind of sex difference in the splenium of the corpus callosum provide little or no grounds for belief in any 'sexual dimorphism'. The possibility remains that in a really large sample of brains, the female splenium might be judged more bulbous on average than the male, but the size of the effect would probably be rather small, certainly within  $d = \pm 0.2$  according to our meta-analyses. Even if such an enormous research project were to find a significant sex difference, the effect could easily arise merely from a difference in brain size and thus have nothing to do with sex per se. Clarke et al. (A17/18; (25)) found that their bulbosity index was correlated with CC area ( $r = -0.47$ ), such that a smaller corpus callosum tended to be more bulbous, irrespective of sex, and they concluded from regression analysis that "for CCs of

equal size, the bulbosity was likely to be the same for men and women" (p. 224). Similarly, a number of studies noted a very high correlation between size of the splenium and the CC as a whole (A12, A17, A30, A35, A37/38, A45; (37,25,4,2,66,26);  $r_s > 0.70$ ), and Demeter et al. (37) concluded "the splenium shows little variability independent of that of the entire CC" (p. 223).

### 3.8. Other parts of the CC

Attention has focused on the splenium because the 1982 *Science* article claimed that was the site of a sex difference. However, several studies subdivided the CC into four or more portions and assessed each for a possible sex difference. Only one region has provided any hint of a consistent effect, although too few studies have yet been reported to allow strong conclusions from a meta-analysis. The area of the isthmus [Fig. 1(A)], defined as the part of the CC adjacent to the splenium and measured as the posterior third of the CC minus the posterior fifth, was significantly larger in males in two studies (A30, A35; (4,2)) but the combined  $d_+ = 0.12$  was not significantly greater than zero for the seven relatively homogeneous values analyzed. Such a small effect, if real, could easily occur because of allometry with brain size.

### 3.9. Handedness and age

The nerve fibers forming the corpus callosum do not connect all regions of the cerebral cortex equally; on the contrary, some zones, especially those that receive primary inputs of sensory data far from the midline of the body, have very few direct connections between the hemispheres (71). Consequently, it is to be expected that specific regions of the CC should be more closely related to certain psychological functions but not others. Likewise, a zone of the CC might differ in a psychologically meaningful way not for the sexes in general but only for specific subgroups within a sex. Subgroup and regional specificity could be present, despite the absence of a generalized sex difference. Three studies (A23, A31, A34; (126,38,55)) have detected a significant interaction between handedness and sex for absolute size of the isthmus, although two others (A36, A45; (115,26)) did not replicate this. In view of continuing controversy concerning the proper measure of handedness in research on neuropsychological deficits ((12,17)) and the small number of reports to date, firm conclusions await further results and evaluation of alternative measures of handedness in relation to CC anatomy.

A sex difference could also be obscured if a change in CC size with age has quite different profiles for males and females. A recent reanalysis of data from Allen et al. (A30; (4)) examined the thickness of seven CC regions for linear, quadratic and cubic trends across age as well as the interaction with sex using analysis of variance (29). Several complex interactions of sex and age trend significant at  $\alpha = 0.05$  were detected. Because the age trends were strongly influenced by inclusion of data for children as young as two years, when the CC is still growing rapidly, the relevance to other studies limited to adults remains to be demonstrated. Driesen and Raz (43), in a meta-analysis of 26 studies that examined age effects on adult corpus callosum area, concluded that CC area decreases slightly

with age, but did not test for differences in this trend for males and females. Of the 14 studies in our meta-analysis that tested for an age effect on corpus callosum area for males and females combined, only three found any significant relationship between age and CC area (A23, A30, A32; (126,4,42)). Only Clarke et al. (A17/18; (25)) tested whether the regression slopes were significantly different for men and women, concluding that they were not ( $p > 0.05$ ). An overall age trend may be due to a cohort effect and would only be important for the analysis of sex differences in the corpus callosum if the ages of the male and female samples were markedly different. We saw no evidence of such a bias in the studies included in this meta-analysis.

## 4. CONCLUSIONS AND RECOMMENDATIONS FOR FUTURE RESEARCH

### 4.1. Corpus callosum and cognitive function

Our review of a substantial literature on the human CC does not support any sex-related difference in the size or shape of the splenium, whether or not adjustments are made for whole brain or cortex size. Because no significant sex difference is established for the splenium, there is no reason to speculate about its possible contribution to cognitive gender differences. The only consistent significant finding is that adult males have a larger average brain size, a fact that has been known for almost a century, and that they also have larger average size of the entire corpus callosum. The functional relevance of this difference in CC area will be difficult to demonstrate when the effect size (0.21) is so small. Cognitive gender differences also tend to be small. Hence, corpus callosum size could mediate the sex effect on thinking only if the correlation between CC size and cognitive performance is nearly perfect, which is not the case (60,63,76,104). Furthermore, it is not at all apparent why minor variations in CC size should affect cognition. A larger CC might have more small diameter axons with thin myelin sheaths, which would increase the number of connections between the hemispheres, or larger and more heavily myelinated axons, which would increase the speed of information transfer. Available evidence suggests no major sex difference in axon size or myelination (1), so both small and large axons may be more common in the larger CC of a larger brain with more neurons. Given that the CC interconnects so many functionally different regions of cerebral cortex (33,85,98), there is no reason to believe that a small difference in overall CC size will pertain to any specific psychological construct. Total absence of the corpus callosum tends to be associated with a ten-point or greater reduction in full-scale IQ, but more specific functional differences from IQ-matched controls are difficult to identify (83), which suggests that specific psychological effects of a minor variation in size within the normal range will be even smaller.

### 4.2. Corpus callosum and brain size

The results of this study also showed that, once brain size has been considered, there are no sex-specific differences in the size of the corpus callosum. It is not surprising that individuals with larger brains also generally exhibit larger corpora callosa ( $r = 0.29$ ) because most body parts tend to grow allometrically or proportionally to the whole (53).

Brain size does not itself determine the size of the corpus callosum, but the size of both may be influenced by a common growth mechanism. Although the fact of a wide variation in brain size within the general population is well established (61), the factors that influence brain size in humans have not been completely determined. An individual's brain size is likely the product of interacting developmental influences, such as sex (61), body size (62), nutrition (89), non-nutritional environment (e.g. maternal alcohol consumption (49)) and age (61). Brain size or weight is the sum of sizes and/or numbers of many components, whether they be viewed as anatomical regions (cerebral cortex, thalamus, cerebellum, etc.) or histological elements (neurons, glia, myelin, blood vessels, etc.). A treatment that affects one component of the CC is also likely to modify whole brain size to some extent. For example, hybrid mice created by mating parents from two inbred strains have larger brains, more myelin and a higher myelin concentration per amount of brain tissue than their parent strains (110). Because the myelin sheath is a major component of the CC, it is therefore no surprise that hybrid mice also have a larger CC or that undernutrition, which impairs myelin formation, also stunts the CC and reduces whole brain size (81). Likewise, hormonal treatments that increase CC size also increase brain size (86). Thus, for a variety of reasons, we should expect to find a modest correlation of brain size and CC size in a genetically heterogeneous population of placental mammals living in a heterogeneous environment.

However, merely knowing that there is a statistical correlation says nothing about why one thing tends to be large when the other is also large. Suppose that certain dietary factors affect whole brain size (89), and early experience affects CC size (10,73), but those dietary factors have no direct impact on CC size. In a human population where a superior diet and enriched experience tend to coincide, there would then be a correlation between brain size and CC size produced by an external environmental correlation rather than physiological correlation. If, on the other hand, the dietary factor influences both brain size and CC size, the correlation will be physiological or developmental. Then, the challenge is to learn whether dietary effects occur via separate developmental pathways or, instead, an effect on one major component of brain size mediates the effect on CC size. Path analysis may help to understand complex covariations, especially in controlled laboratory situations (24), but data on humans are sometimes inadequate for this purpose (51). Suitable information on the human CC is undoubtedly lacking at the present time, although progress in understanding sex differences in the CC has been made with animal models (73,77).

#### 4.3. Interpreting significant findings

If and when a significant association between the size of a brain structure and some psychological measure is confirmed, this is not a sufficient reason to conclude that the specific brain variation caused the psychological change. Every good psychology student knows that correlation does not prove causation. In one recent study, a modest correlation between cerebrum size and IQ within a sex was detected (5). At the same time, males and females differ substantially in brain size but not IQ. There could

easily be some third factor or array of processes that acts to increase both brain size and IQ score for people of the same sex, even though brain size per se does not mediate the effect of the other factor on IQ. Proof of a causal relation requires converging evidence from a variety of sources and, if at all possible, experimental intervention such as surgical section of a portion of the CC. In this respect, cognitive neuroanatomy is barely in its infancy because consistent correlation is still being sought. Without a convincing correlation, the question of causation need not be debated.

#### 4.4. Publication and literature review bias

If there is a tendency for researchers and/or editors of scholarly journals to publish reports of significant sex differences and neglect reports of no difference, the combined estimate of effect size in meta-analysis will be biased upwards. Although the journal *Science* has refused to publish failures to replicate the 1982 claims of de Lacoste-Utamsing and Holloway (Byne, personal communication), many failures to replicate have found their way into the world literature, especially neurology journals. Negative findings are often published in miniature, such as the terse, four sentence results sections of Oppenheim et al. (96) and Weis et al. (122). Nevertheless, they are an important part of the total picture, provided that the methodology is acceptable. Possible publication bias may be tested by plotting sample size against effect size for each study (23). The distribution is expected to resemble an inverted funnel because effect sizes from larger samples are expected to match more closely the true underlying population value. Plots for corpus callosum and splenial areas closely resemble inverted funnels and are not indicative of publication biases (Fig. 3). The plot for splenial width is skewed mainly because of two exceptionally large negative values. Given the large number of non-significant sex differences in the literature on the human corpus callosum, we surmise that our meta-analysis on this topic is not substantially distorted by publication bias in the scientific literature as a whole.

Bias in the literature review can also distort the meta-analysis, and every effort should be made to ferret out articles in the most obscure journals or even abstracts from conference presentations. It is completely unacceptable to highlight only positive differences published in prestigious journals, while ignoring contrary data elsewhere. Prestige is no guarantee of truth. Any single research project, no matter how well controlled, can fall victim to Type I error, as happened recently for claims of major genes for manic-depressive psychosis and schizophrenia. Prestige is associated with readership of the journal, and for this reason, it is not surprising that citation counts vary widely for articles in our review. Before February 1993, the 1982 *Science* article that initiated the controversy had been cited over 127 times, according to the Science Citation Index, whereas one failure to replicate in 1991 had never been cited at all (45), and several other papers had been cited twice or less per year. Despite the very wide range of citation rates, the correlation between citation rate and effect size for splenial width (Spearman  $r = -0.20$ ,  $t = -0.77$ ,  $p > 0.05$ ) does not suggest a pervasive bias in citations in the literature. However, perhaps a more important consideration should be the publicity that a finding receives in general interest

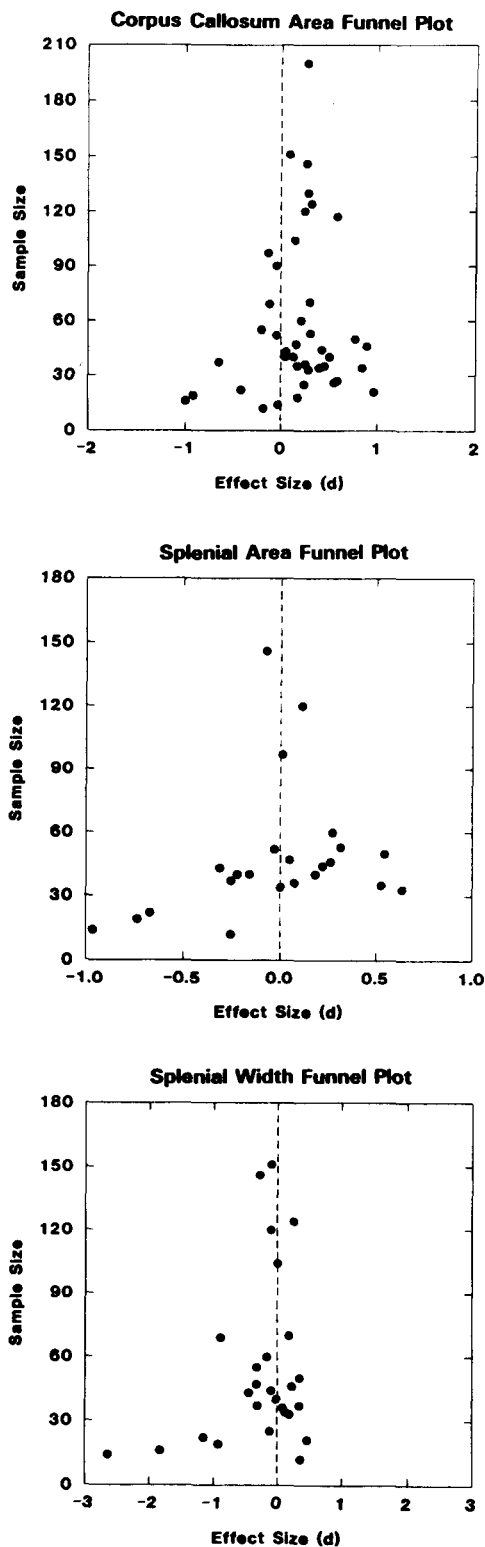


FIG. 3. Funnel plots of corpus callosum area, splenial area, and splenial width. Plotting sample size against effect size should result in an inverted funnel shape if no publication bias exists. The dotted line indicates an effect size of zero. Plots suggest that no substantial bias existed in the publication of results. Skewness for splenial width was present because of two extreme negative values that expanded the  $x$ -axis.

journals, newspapers and magazines. From the rate at which we have discovered studies that were missed in our initial literature review, especially those concerned with schizophrenia, we surmise that there are probably more than 49 published papers from 1982 to 1994, but the omissions are not likely to alter our conclusions.

#### 4.5. Cumulative meta-analysis

When many small-scale studies of small effects are published, the chances are good that a few will report a statistically significant sex difference. Unfortunately, some people tend to confer far more meaning on such 'positive' findings than they warrant. If there is a bias among journalists in favor of reporting sex differences in the mass media and ignoring articles finding no differences, this could easily propagate a myth bolstered by apparent scientific legitimacy. One of our local newspapers has indeed printed claims promulgated over wire services about new studies finding a sex difference in the corpus callosum (11,15) but has yet to print a word about contrary findings which, as we have shown, far outnumber the statistically significant differences. Recent review articles in popular science media have done little or nothing to counteract the myth. Kimura (78) emphasized the claims of de Lacoste-Utamsing and Holloway (34) by name, mentioning that they had been "both refuted and confirmed" by anonymous persons, and "most recently" replicated by Allen et al. (4), which gives a definite impression that the weight of the literature favors a sex difference when, as we have shown, the complete literature does not. LeVay (84) also mentioned that several studies failed to replicate the 1982 report but then proclaimed that Allen et al. (4) used "advanced imaging techniques...[to]...confirm the original report", despite the fact that 12 previous MRI studies had not confirmed it.

We believe that the glaring discrepancy between messages in the scientific literature and the popular science media could be prevented to some extent if each team of investigators carried out a thorough review of previous publications and conducted their own meta-analysis of the literature, including their current findings. The big issue is not whether an individual study finds positive results; rather, we want to know how much the combined estimate of effect size  $d_+$  changes because of the latest addition to the literature (108). The gold-standard in the medical literature is a cumulative meta-analysis conducted using the raw data. We urge investigators to make their raw data or, better yet, the actual tracings available for cumulative meta-analysis. We attempted to collect the raw data from studies of sex differences in the CC cited in an earlier version of this paper (120) by writing to the authors. The level of response was astoundingly poor. In several studies that used MRI, the authors even stated that the original observations were no longer available. Hence, cumulative meta-analysis from summary statistics becomes necessary. We have written a simple computer program that makes meta-analysis of a series of two-group studies very easy. Starting with the 1982 article in *Science*, we have updated the estimate of  $d_+$  for the size of the splenium of the corpus callosum with each

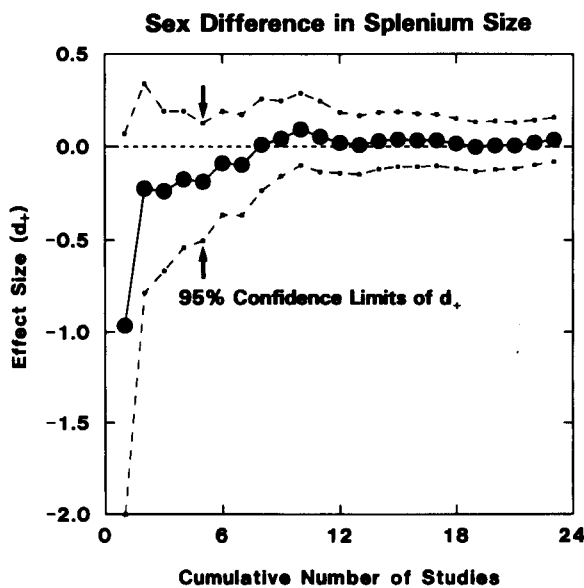


FIG. 4. Cumulative meta-analysis of size of the splenium of the corpus callosum. The combined estimate of effect size  $d_+$  and its 95% confidence limits are recomputed after the addition of each new study in chronological order to the world literature on this topic. The first article (34) found a large but non-significant difference in favor of females, but no subsequent investigation observed anything even close to it. The seventh report (A18; (25)) moved  $d_+$  close to zero, where it has remained. The confidence limits have gradually become narrower as more information has been added.

subsequent article listed in Table A2. As shown in Fig. 4, the combined effect size hovered slightly but not significantly below zero (female splenium larger) for the first few studies. Gradually, the best estimate of effect size approached zero, and the confidence limits became narrower. After the seventh study was reported in 1989, the jury returned a verdict of no significant sex difference and then never found cause to reopen the case because of new evidence. Given the magnitude of sex difference in the splenium in previous reports, the possibility that further studies would alter this conclusion seems remote.

#### 4.6. When to halt research on a topic

It is very difficult to specify when research on a topic should cease because of disappointing results (e.g. (20)). We do not propose that further research on a particular kind of sex difference be halted as soon as the confidence interval for effect size includes zero. As Fig. 4 shows, when relatively few studies have been carried out, one or two positive results can nudge  $d_+$  towards significance. After a much longer series, it seems pointless to continue until the confidence interval is so narrow that the genuine lack of any effect is apparent. For splenium size, even after 23 studies, the confidence interval, while including zero, also allows for an effect size of 0.15. Perhaps the most reasonable stopping point should be decided by the smallest effect size that one considers worthy of serious attention in the field of study. Cohen's (27) suggestion, that  $\delta = 0.2$  is a small effect in psychology, seems to be a reasonable criterion. The 95% confidence interval for  $\delta$  shrunk within the  $\pm 0.2$  limits after 12 studies of the splenium of the CC. Although an effect that is small statistically is not necessarily

theoretically uninteresting, a worthy effect size can be operationally defined by the sample sizes traditionally used in a field of study. The average group sample size for the 49 studies in this meta-analysis was 30. This sample size is sufficient to detect a moderate effect size of  $\delta = 0.75$  with a statistical power of 80%. On the other hand, to detect an effect size of  $\delta = 0.2$  with 80% power using a two-tailed test with  $\alpha = 0.05$  requires 395 subjects per group (119). Because all of the sample sizes reported in the literature on sex differences in the corpus callosum are considerably less than 400 of each sex, we suspect that our colleagues are really not very interested in finding such small effects.

It would be unwise to engage in further research on this topic unless a large enough sample is used in a single study to make the test sufficiently sensitive to the small effects that prevail in this domain. As indicated in Table 2, no true sex difference in the corpus callosum is likely to exceed  $\delta = 0.25$ . The numbers of brains of each sex needed to test for a variety of small effects with a power of 80% are given in Table 2. The bare minimum would be 300 men and 300 women. An adequate sample size may be readily attained through a collaborative effort between researchers, but conducting and publishing single studies with grossly inadequate power are not good scientific practice. Whether the quest for such minuscule sex differences is worth the cost of time on an MRI machine is debatable, but additional studies of sex differences using samples one-tenth the appropriate size will contribute correspondingly little to our understanding of brain function.

It is possible that improved measurement techniques or statistical control for a formerly unsuspected factor might lead to the resurrection of a deceased hypothesis. Caution is warranted, of course, because sampling error can yield a deceptively large effect in one study, even after many negative reports. Does the new report of a large sex difference merely add another entry to our meta-analysis, or does it herald a new era of consistently large effects? If the methodology is, indeed, new and improved, the report could form the starting point of a new series to be subjected to meta-analysis after several attempts at replication by other investigators, thereby avoiding submergence by the heavy weight of prior evidence.

#### 4.7. Criterion for statistical significance

By convention, we are taught that the null hypothesis of no sex difference should be rejected if the probability of erroneously rejecting the null on the basis of a set of data is 5% or less. If 10 independent measures are analysed in one study, each with the  $\alpha = 0.05$  criterion, the probability of finding at least one 'significant' sex difference by chance alone is  $1 - (1 - 0.05)^{10} = 0.40$  or 40%. Consequently, when  $J$  tests involving the same object, e.g. the corpus callosum, are done in one study, the criterion for significance of each test might better be adjusted to  $\alpha/J$ , the Dunn or Bonferroni criterion that is described in many textbooks. All but two of 49 studies of the CC adopted  $\alpha = 0.05$  or even 0.10, and for 45 of these studies, an average of 10.2 measures were assessed with independent tests. Only Allen et al. (4) used the Bonferroni criterion, and Johnson et al. (72) employed  $\alpha = 0.001$  to correct for "the large number of degrees of freedom in the sample size". It is no wonder that the literature on neural sex differences is so contaminated by

false positive results that cannot be replicated. The Dunn/Bonferroni adjustment may be too conservative when a really thorough analysis is carried out because the more complete the analysis, the harder it will be to detect any particular effect. A more accurate alternative would be multivariate analysis (90) with simultaneous confidence intervals for each measure of the corpus callosum, which does not make the unlikely presumption that the measures are independent. Five studies (A14, A23, A36, A43, A46;(106,126,115,131,63)) utilized a multivariate analysis, but all followed up with univariate tests at  $\alpha = 0.05$ , thereby negating the benefits of the multivariate procedure.

#### 4.8. The social responsibility of scientists

Although much of the blame for the appalling public misconceptions about sex differences in the corpus callosum undoubtedly resides with journalists who selectively attend to 'positive' findings and news editors who welcome confirmation of their belief in biologically based cognitive

gender differences, scientists should also accept some responsibility for the making of a myth. Of course, none of us is culpable when Phil Donahue confuses a neuron and an axon. Nevertheless, much can and should be done to avoid further littering of scientific journals with false claims of sex differences. Cumulative meta-analysis of effect size, use of a more stringent significance criterion and sample size determination by power analysis are well established methods to elevate the quality of our science.

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## APPENDIX

## A. Summary of subjects and methods in modern studies

TABLE A1

Number	Study	Method	Subjects	Sex	Subject variables		Age (years)	Hand	Measurement variables			
					n	Sex			Splenium defined method	Splenium width method	Splenium shape method	
A1.	de Lacoste-Utamsing and Holloway (1982)	Post-mortem	Autopsy	m	9	nr	nr		P5	nr	Maximum width	Classify by sex
A2.	Bell and Variend (1985)	Post-mortem	Autopsy	f	5	nr	0-12		P5	Straight line	Maximum width	Classify by sex
A3.	de Lacoste et al. (1986)	Post-mortem	Autopsy fetuses	f	16	0-14	26-41 weeks		P5	Curved line	Maximum width	
A4.	Holloway and de Lacoste (1986)	Post-mortem	Cadavers	m	13	26-41 weeks	26-41 weeks		nr	nr	Maximum width	
A5.	Nasrallah et al. (1986)	MRI	RH normal controls	f	8	73.0	nr	all RH	P4	Bent line	P4 boundary	
A6.	Weber and Weis (1986)	Post-mortem	Autopsy	f	10	72.85	72.85		P5	Straight line	Max. horiz. diameter	Form area
A7.	Yoshii et al. (1986)	MRI	Normal controls	f	18	76.58	76.58		P5	nr		Classify by sex
A8.	Kertesz et al. (1987)	MRI	Normal scans	m	14	Combined	Combined	28 RH and 5 LH/MH	nr	nr		Classify by sex
A9.	Oppenheim et al. (1987)	MRI	Medical patients	f	19	24-82	24-82		% CC in P5	Straight line	Max. vert. diameter	Classify by sex
A10.	Simon et al. (1987)	MRI	Adult controls	m	51	Combined	Combined	52 RH and 52 LH	nr	nr		Classify by sex
A11.	Byne et al. (1988)	MRI	Normal scans	f	53	18-49	18-49					Classify by sex
A12.	Demeter et al. (1988)	Post-mortem	Autopsy	m	40	nr	nr		P5	nr	Maximum width	Circularity
A13.	O'Kusky et al. (1988)	MRI	Normal and epilepsy	f	22	64	64		P5	Curved line	Maximum width	Classify by sex
A14.	Reinartz et al. (1988)	MRI	Normal volunteers	m	12	58	58	54 RH, 25LH, 21 MH	P5	Bent line	P5 boundary	
A15.	Takeda et al. (1988)	MRI	Adults	f	49	11-60	11-60	40 RH and 40 LH	% CC in P4	Straight line		Classify by sex
A16.	Weis et al. (1988)	MRI	Normal scans	m	40	19-40	19-40		nr	nr	Maximum width	
A17.	Clarke et al. (1989)	Post-mortem	Autopsy adults	f	79	Combined	Combined		P5	Straight line	Max. vert. diameter	Bulbosity classify
				m	72	20-78	20-78		P5	Radial gravity	Largest of 10 widths	
				f	20	44.1	44.1					
				f	26	48.9	48.9		P5			
				m	27	nr	nr					
				f	19	nr	nr					

TABLE A1  
CONTINUED

Number	Study	Method	Subjects	Sex	Subject variables		Age (years)	Hand	Measurement variables			Splenium shape method
					n	Sex			Splenium defined	Splenium area	Splenium width	
A18.	Clarke et al. (1989)	MRI	Adults	m	5	nr			P5	Radial gravity	Largest of 10 widths	Bulbosity classify
A19.	Hauser et al. (1989)	MRI	Normal controls	m	7	nr				Bent line	P4 boundary	
A20.	Hayakawa et al. (1989)	MRI	Adult patients	f	11	37.0						
A21.	Prokop et al. (1989)	Post-mortem	Autopsy	m	13	Combined 21-40		17 RH, 6 LHand 2 unknown	% CC in P4			
A22.	Prokop et al. (1989)	MRI	Patients	f	34	78			% CC in P5	Straight line	Max. vert. diameter	
A23.	Witelson (1989)	Post-mortem	Cancer patients	m	29	37			% CC in P5	Straight line	Max. vert. diameter	
A24.	de Lacoste et al. (1990)	Post-mortem	Autopsy	f	26	46				Straight line	Maximum width	
A25.	Elster et al. (1990)	MRI	Normal scans	m	15	50.0		32 CRH and 18 NCRH	P5	Straight line	Maximum width	
A26.	Going and Dixson (1990)	Post-mortem	Cadavers	f	35	51.0				nr	Maximum width	Form area
A27.	Holloway (1990)	Post-mortem	Autopsy	f	36	60						
A28.	Okamoto et al. (1990)	MRI	Normal volunteers	m	33	57		All RH	P5	Observation and str.-line	Maximum width	
A29.	Raine et al. (1990)	MRI	Normal controls	f	60	38.1						
A30.	Allen et al. (1991)	MRI	Normal scans	f	17	74.4		All RH	P5	nr	Maximum width	
A31.	Denenberg et al. (1991)	MRI	Normal scans	f	16	82.0						
A32.	Doraiswamy et al. (1991)	MRI	Normal volunteers	m	13	nr				Straight line	Maximum width	Bulbosity classify
A33.	Emory et al. (1991)	MRI	Normal controls	f	9	nr				Straight line	Maximum width	
A34.	Habib et al. (1991)	MRI	Normal scans	m	17	Combined						
A35.	Aboitiz et al. (1992b)	Post-mortem	Hospital admissions	f	10	18-31				Bent line	P4 boundary	Classify by shape
				f	9	34.1						
				m	73	36.6				Straight line	Maximum width	Bulbosity classify
				f	73	36.5						
				m	51	Combined 18-49		52 RH and 52 LH	P10	99 widths	99 widths	
				f	53	53		All but 4 RH				
				m	15	56						
				f	20	Combined 20-43		All RH	P5	nr		Classify by shape
				m	20	48.5						Bulbosity
				f	35	Combined		26 CRH and 27 NCRH	P5	Radial gravity		
				m	18	18-51						
				f	20	45.1		All RH	P5	Straight line		

Number	Study	Method	Subjects	Sex	Subject variables		Age (years)	Hand	Splenum defined	Measurement variables		
					n	Sex				Splenum area method	Splenum width method	Splenum shape method
A36.	Steinmetz et al. (1992)	MRI	Healthy adults	m	26	Combined	19 CRH, 24 MH, and 9 CLH	P5	Straight line			
A37.	Holloway et al. (1993)	Post-mortem	Mt Sinai autopsy	f	26	21-35		P5	Straight line	Maximum width		
A38.	Holloway et al. (1993)	Post-mortem	Columbia autopsy	f	26	66.6		P5	Straight line	Maximum width		
A39.	Holloway et al. (1993)	Post-mortem	Australian autopsy	f	23	62.7		P5	Straight line	Maximum width		
A40.	Laissey et al. (1993)	MRI	Normal controls	f	10	35.4		nr	nr	nr		
A41.	Pujol et al. (1993)	MRI	Normal scans	f	61	37.3						
A42.	Woodruff et al. (1993)	MRI	Normal controls	f	29	37.6						
A43.	Wu et al. (1993)	MRI	Normal controls	f	61	29		P4	Straight line	P4 boundary		
A44.	Burke and Yeo (1994)	MRI	Elderly persons	f	34	30	29 RH; 4 LH and 1 MH	P4	Straight line	P4 boundary		
A45.	Clarke and Zaidel (1994)	MRI	Graduate students	f	10	nr		P5	Bent line	P4 boundary		
A46.	Hoff et al. (1994)	MRI	Normal controls	f	9	Combined	all RH	P5	Straight line	Maximum width		
A47.	Johnson et al. (1994)	MRI	Normal volunteers	f	7	30.5		P5	Straight line			
A48.	Pozzilli et al. (1994)	MRI	Normal scans	f	38	77.9	5% LH and 8% MH	P5	Straight line			
A49.	Rauch and Jinkins (1994)	MRI	Normal adults	f	59	77.7		P5	Straight line	Maximum width		
					30	Combined	30 RH and 30 LH	P5	Straight line	Maximum width		
					30	28.2		P5	Straight line			
					20	27.9	31 RH and 4 LH	P5	Straight line			
					15	27.3						
					100	Combined						
					100	16-65		P4	Straight line			
					53	Combined						
					77	42						
					56	35						
					61	36						

All studies are independent, except that of Kertesz and Denenberg, who analyzed the same brains using different methods.

nr: not reported, but was measured.

blank space: not measured.

MRI: magnetic resonance imaging.

P5: posterior fifth.

P4: posterior fourth.

P10: posterior tenth.

RH: right-handed.

LH: left-handed.

MH: mixed-handed.

CRH: consistent right-handed.

CLH: consistent left-handed.

NCRH: non-consistent right-handed.

## B. Summary of measurements from modern studies

TABLE A2

Study number	Measurement	Male mean (n)	Female mean (n)	Pooled SD	Two-tailed <i>p</i>	Estimate <i>d</i>
A1.	Brain weight	1379.4 (9)	1205.0 (5)	123.3	0.026	+ 1.3244
	CC area	704.3 (9)	708.3 (5)	126.7	0.956	- 0.0295
	Splenial area	186.1 (9)	218.3 (5)	31.2	0.089	- 0.9647
	Splenial width	11.4 (9)	16.4 (5)	1.8	0.000	- 2.6489
A2.	CC area	nr (28)	nr (16)	nr	> 0.050(m > f)	na
	Splenial area	nr (28)	nr (16)	nr	> 0.050(m > f)	na
	Splenial width	nr (28)	nr (16)	nr	< 0.050(m > f)	na
A3.	Brain weight	272.1 (19)	260.2 (13)	nr	0.575	+ 0.1986
	CC area	52.7 (19)	62.0 (13)	13.0	0.130	- 0.6905
	Splenial width	2.6 (19)	3.4 (13)	0.8	0.013	- 0.9257
A4.	Brain weight	1248.0 (8)	1202.0 (8)	150.1	0.549	+ 0.2897
	CC area	618.4 (8)	744.4 (8)	119.5	0.053	- 0.9960
	Splenial width	10.3 (8)	13.3 (8)	1.5	0.002	- 1.8290
A5.	CC area	705.0 (11)	605.0 (10)	98.9	0.032	+ 0.9703
	Splenial width	6.1 (11)	5.2 (10)	1.8	0.279	+ 0.4675
A6.	Brain weight	1029.5 (18)	890.3 (18)	112.4	0.001	+ 1.2108
	CC area	639.5 (18)	613.3 (18)	103.0	0.451	+ 0.2487
	Splenial area	164.5 (18)	162.4 (18)	28.5	0.826	+ 0.0720
	Splenial width	14.9 (18)	14.8 (18)	1.2	0.800	+ 0.0831
A7.	CC area	nr (14)	nr (19)	nr	> 0.050	na
	Splenial area	nr (14)	nr (19)	nr	> 0.050	na
A8	CC area	724.0 (51)	716.0 (53)	nr	> 0.050	na
A9.	Splenial area/CC area	30.4%(40)	31.2%(40)	3.7%	0.341	- 0.2121
	Splenial width/CC	23.7%(40)	24.1%(40)	3.4%	0.605	- 0.1150
A10.	Length					
A11.	CC area	641.0 (17)	561.0 (17)	92.5	0.017	+ 0.8443
	CC area	519.0 (15)	601.0 (22)	123.2	0.055	- 0.6511
	Splenial area	160.0 (15)	170.0 (22)	37.7	0.434	- 0.2590
A12.	Splenial width	10.7 (15)	11.5 (22)	2.5	0.346	- 0.3131
	CC area	627.0 (22)	582.0 (12)	111.7	0.270	+ 0.3932
	Splenial area	165.0 (22)	165.0 (12)	32.6	1.000	0.0000
	Splenial width	11.8 (22)	11.6 (12)	1.6	0.730	+ 0.1218
A13.	CC area	nr (49)	nr (51)	nr	0.260	na
	Splenial area	nr (49)	nr (51)	nr	> 0.050	na
	Splenial width	nr (49)	nr (51)	nr	> 0.050	na
A14.	Splenial area/CC area	33.3%(40)	34.8%(40)	2.7%	0.016	- 0.5433
A15.	CC area	549.6 (79)	542.5 (72)	84.9	0.608	+ 0.0832
	Splenial width	11.0 (79)	11.2 (72)	1.9	0.511	- 0.1068
A16.	CC area	669.9 (20)	665.2 (20)	110.2	0.893	+ 0.0420
	Splenial area	191.5 (20)	199.9 (20)	36.3	0.469	- 0.2269
	Splenial width	13.1 (20)	13.1 (20)	1.8	0.945	- 0.0215
A17.	CC area	680.0 (27)	590.0 (19)	98.8	0.004	+ 0.8950
	Splenial area	173.0 (27)	165.0 (19)	30.0	0.378	+ 0.2621
	Splenial width	11.1 (27)	10.7 (19)	1.8	0.457	+ 0.2210
A18.	CC area	540.0 (5)	550.0 (7)	50.0	0.740	- 0.1846
	Splenial area	148.0 (5)	152.0 (7)	14.3	0.643	- 0.2586
	Splenial width	10.8 (5)	10.3 (7)	1.3	0.521	+ 0.3595
A19.	CC area	570.0 (14)	550.0 (11)	78.9	0.540	+ 0.2421
	Splenial area/CC area	nr (14)	nr (11)	nr	0.0008(m > f)	+ 1.4960
	Splenial width	4.9 (14)	5.1 (11)	1.6	0.756	- 0.1227
A20.	CC area	673.0 (13)	624.0 (13)	86.0	0.159	+ 0.5517
A21.	CC area	634.2 (36)	600.2 (34)	112.5	0.211	+ 0.2989
	Splenial area/CC area	25.1%(36)	25.8%(34)	3.0	0.528	- 0.1692
	Splenial width	8.5 (36)	8.4 (34)	0.5	0.446	+ 0.1815
A22.	CC area	603.1 (29)	627.4 (26)	116.4	0.443	- 0.2058
	Splenial area/CC area	29.1%(29)	29.6%(26)	2.8	0.316	- 0.2389
	Splenial width	8.3 (29)	8.4 (26)	0.4	0.222	- 0.3291
A23.	Brain weight	1439.0 (15)	1263.0 (35)	99.2	0.000	+ 1.7463
	CC area	719.2 (15)	656.6 (35)	79.9	0.014	+ 0.7722
	Splenial area	188.4 (15)	173.3 (35)	27.3	0.079	+ 0.5435
	Splenial width	13.5 (15)	12.7 (35)	2.3	0.262	+ 0.3446
A24.	Isthmus area	66.1 (15)	65.1 (35)	13.5	0.812	+ 0.0728
	Brain weight	1232.0 (36)	1129.0 (33)	124.3	0.001	+ 0.8193
	CC area	619.9 (36)	637.2 (33)	143.8	0.619	- 0.1191
	Splenial width	11.6 (36)	13.5 (33)	2.2	0.0004	- 0.8906
A25.	CC area	719.0 (60)	692.0 (60)	109.7	0.180	+ 0.2444
	Splenial area	208.0 (60)	204.0 (60)	35.4	0.537	+ 0.1123
	Splenial width	12.2 (60)	12.4 (60)	1.9	0.555	- 0.1073

TABLE A2  
CONTINUED

Study number	Measurement	Male mean ( <i>n</i> )	Female mean ( <i>n</i> )	Pooled SD	Two-tailed <i>p</i>	Estimate <i>d</i>
A26.	CC area	656.0 (17)	621.0 (16)	121.6	0.415	+ 0.2808
	Splenial area	192.0 (17)	170.0 (16)	33.7	0.071	+ 0.6363
A27.	Splenial width	11.5 (17)	11.1 (16)	2.1	0.579	+ 0.1905
	CC area	703.1 (13)	765.6 (9)	145.2	0.333	- 0.4141
	Splenial area	137.7 (13)	158.9 (9)	30.4	0.124	- 0.6700
A28.	Splenial width	12.3 (13)	14.3 (9)	1.7	0.012	- 1.1557
	CC area	700.9 (17)	648.3 (10)	86.8	0.141	+ 0.5874
A29.	Splenial width	12.6 (17)	12.1 (10)	1.4	0.375	+ 0.3490
	CC area	590.0 (9)	570.0 (9)	108.2	0.719	+ 0.1748
A30.	Splenial width	nr (9)	nr (9)	nr	nr( <i>m</i> > <i>f</i> )	na
	CC area	681.0 (73)	663.0 (73)	68.9	0.117	+ 0.2600
	Splenial area	188.0 (73)	190.0 (73)	25.6	0.638	- 0.0776
	Splenial width	12.5 (73)	13.0 (73)	1.7	0.079	- 0.2910
A31.	Isthmus area	67.0 (73)	64.0 (73)	8.5	0.036	+ 0.3493
	CC area	728.5 (51)	712.7 (53)	111.1	0.470	+ 0.1411
	Splenial width	8.6 (51)	8.6 (53)	1.8	0.987	- 0.0032
A32.	CC area	572.0 (15)	555.0 (20)	100.6	0.624	+ 0.1652
A33.	CC area	452.0 (20)	443.0 (20)	69.8	0.686	+ 0.1263
A34.	Splenial area	172.0 (20)	177.0 (20)	30.0	0.601	- 0.1633
	CC area	809.6 (35)	775.6 (18)	110.0	0.292	+ 0.3045
	Splenial area	212.9 (35)	201.4 (18)	36.0	0.276	+ 0.3145
A35.	Isthmus area	86.0 (35)	83.7 (18)	19.6	0.686	+ 0.1160
	CC area	659.0 (20)	616.0 (20)	84.1	0.114	+ 0.5014
	Splenial area	170.0 (20)	165.0 (20)	27.1	0.562	+ 0.1814
A36.	Isthmus area	60.0 (20)	52.0 (20)	12.2	0.044	+ 0.6445
	CC area	673.0 (26)	678.0 (26)	103.1	0.862	- 0.0478
	Splenial area	182.0 (26)	183.0 (26)	30.5	0.906	- 0.0323
A37.	Isthmus area	61.0 (26)	67.0 (26)	15.0	0.156	- 0.3931
	Brain weight	1373.0 (21)	1175.0 (26)	116.5	0.000	+ 1.6713
	CC area	664.0 (21)	651.0 (26)	82.5	0.594	+ 0.1550
A38.	Splenial area	176.0 (21)	175.0 (26)	20.9	0.871	+ 0.0471
	Splenial width	12.1 (21)	12.6 (26)	1.5	0.254	- 0.3335
	Brain weight	1357.0 (20)	1245.0 (23)	143.2	0.014	+ 0.7675
	CC area	611.0 (20)	605.0 (23)	121.8	0.873	+ 0.0484
A39.	Splenial area	150.0 (20)	160.0 (23)	31.1	0.299	- 0.3157
	Splenial width	10.7 (20)	11.4 (23)	1.5	0.135	- 0.4581
	Brain weight	1021.0 (9)	939.0 (10)	82.0	0.044	+ 0.9551
	CC area	545.0 (9)	635.0 (10)	93.9	0.052	- 0.9156
A40.	Splenial area	138.0 (9)	154.0 (10)	20.8	0.113	- 0.7345
	Splenial width	10.3 (9)	11.7 (10)	1.4	0.050	- 0.9271
	CC area	654.0 (63)	617.0 (61)	117.0	0.081	+ 0.3142
A41.	Splenial width	11.0 (63)	10.6 (61)	1.6	0.156	+ 0.2549
A42.	CC area	576.8 (29)	582.0 (61)	99.0	0.815	- 0.0526
A43.	CC area	707.8 (34)	665.2 (10)	99.1	0.239	+ 0.4221
	Splenial area	231.6 (34)	222.5 (10)	40.6	0.537	+ 0.2201
	Splenial width	7.0 (34)	7.2 (10)	1.9	0.765	- 0.1062
A44.	CC area	nr (9)	nr (7)	nr	> 0.050	na
	Splenial area	nr (9)	nr (7)	nr	> 0.050	na
	Splenial width	nr (9)	nr (7)	nr	> 0.050	na
A45.	CC area	555.5 (38)	568.1 (59)	90.4	0.504	- 0.1383
	Splenial area	158.6 (38)	158.3 (59)	30.9	0.967	+ 0.0087
	Isthmus area	67.4 (38)	65.6 (59)	22.6	0.706	+ 0.0782
A46.	CC area	687.5 (30)	669.9 (30)	83.3	0.417	+ 0.2086
	Splenial area	205.4 (30)	198.2 (30)	26.1	0.289	+ 0.2728
	Splenial width	12.3 (30)	12.5 (30)	1.4	0.505	- 0.1710
A47.	Isthmus area	55.1 (30)	58.5 (30)	11.9	0.274	- 0.2818
	CC area	538.0 (20)	505.0 (15)	72.2	0.190	+ 0.4469
	Splenial area	151.0 (20)	139.0 (15)	22.3	0.128	+ 0.5258
A48.	CC area	670.0 (100)	644.0 (100)	98.1	0.062	+ 0.2641
A49.	CC area	709.0 (53)	678.0 (77)	110.0	0.117	+ 0.2802
	Splenial area	nr (53)	nr (77)	nr	> 0.050	na
	CC area	580.0 (56)	530.0 (61)	85.7	0.002	+ 0.5798

All weights are in grams, all areas are in square millimeters, and all widths are in millimeters.

nr: measured, but not reported.

na: not able to calculate the statistic from the information given in the study.