

# Brain size: a possible source of interindividual variability in corpus callosum morphology<sup>1</sup>

Lutz Jäncke<sup>1</sup> and Helmuth Steinmetz<sup>2</sup>

<sup>1</sup> Institute of General Psychology,  
Otto-von-Guericke-University Magdeburg, Germany

<sup>2</sup>Department of Neurology,  
University of Frankfurt, Germany

## Introduction

The corpus callosum (CC) is the main fiber tract connecting the cerebral hemispheres, and it has been estimated that about 200-350 million fibers run through this structure in the human brain (1,2). The CC seems to be important in the transfer and facilitation of associative information between the hemispheres. It is thought that the cross-sectional size of the CC may indicate the number of fibres crossing through (1), implying that a larger callosal area may indicate a higher capacity for interhemispheric transfer. Because the midsagittal CC size is so easy to measure either in post mortem material or on magnetic resonance images (MRI) it is one of the human brain structures to receive particular attention. There is some evidence suggesting that the morphology of the CC may be related to language dominance (13,14), gender (19), handedness (71,73-75), Down's syndrom (68), dysphasia (51), schizophrenia (76), and dyslexia (32). The sometimes conflicting results in CC morphology were interpreted in two ways. The common interpretation has been that a larger CC midsagittal area (total CC or CC subarea) reflects increased interhemispheric connectivity resulting in (or due to) increased ambilaterality (73). This interpretation is at variance with the interpretation by Clarke and Zaidel (13) that the CC size indicates the amount of fibers inhibiting or interfering processes located in the dominant hemisphere. In the light of these controversies and with respect to the enormous variability in CC size across the subgroups tested, we employed whole-brain in-vivo magnetic resonance morphometry in order to investigate the anatomical relationship between CC midsagittal size and forebrain volume (FBV). This approach may also provide an empirical evaluation of the recently suggested relationship between brain size and lateralization (61) and it might help to explain the large interindividual variability in callosal size. In particular, we were interested to answer the following questions: (i) Is there an allometric relation between callosal size and brain size; (ii) If there is a relation between callosal size and brain size does this relation follow a geometrical rule?; (iii) Is there a true influence of gender? and (iv); Is handedness or brain lateralization related to callosal size?

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<sup>1</sup> Correspondence should be addressed to Dr. Lutz Jäncke, Ph.D., Institute of General Psychology, Otto-von-Guericke-University Magdeburg, Germany, Lennéstr. 6, 39112 Magdeburg, lutz.jaencke@gse-w.uni-magdeburg.de

## The relation between corpus callosum size and forebrain volume

Several attempts have been undertaken to relate brain and CC size measures in humans. In general, most postmortem studies found small but significant linear correlations between both measures (3,71,73, 78). However, recent large studies using MRI to estimate brain size by one or a few cross-sectional brain area measures revealed no significant CC/brain size relation (15,45,58). These results were taken as evidence for a lack of an allometric CC/brain size relationship. In our own study (39) we measured forebrain volume and the size of the midsagittal CC area in 120 young and healthy adults (49 women, 71 men, mean age  $\pm$  S.D. =  $25.7 \pm 4.7$  years) using in-vivo magnetic resonance morphometry of the brain (128 contiguous sagittal 1.17mm-thick sections). In this study we found a mean  $\pm$  S.D. total brain volume of  $1.120 \pm 0.110$  liter for women and  $1.240 \pm 0.110$  liter for men. Taking into account a specific gravity of fresh postmortem brain tissue of 1.04-1.09 kg/liter (10), and the up to 9% increase in brain volume during the first hours after death (presumably due to the absorption of cerebrospinal fluid) (6), our brain volume measurements obtained in living subjects correspond exactly to what one would expect from these postmortem data. With these in vivo measurements of brain volume we evaluated the CC/brain volume relationship. Because total brain volume is mostly determined by forebrain volume (brain volume - hindbrain volume) the following analysis is focused on forebrain volume (FBV).

When relating midsagittal CC size to FBV one has to consider that CC size is measured as an area ( $\text{mm}^2$ ) and FBV as a volume ( $\text{mm}^3$ ). In addition, CC area is part of the FBV and, thus, contributes to FBV. As a first approach in relating CC size to FBV one might argue that brains of different size are geometrically similar. In Euclidean geometry, two triangles are geometrically similar if corresponding sides are in a constant ratio and corresponding angles are equal. In addition, if two triangles are equiangular, then their corresponding sides are proportional. Such geometric similar bodies are often called isometric. The same considerations pertain to any other geometrically similar figures and can be extended to three-dimensional figures as well. Now consider two cubes of different sizes. Because all corresponding linear measurements of the two cubes are in the same proportion and all corresponding angles are equal, the two cubes are geometrically similar or isometric. The surface area of the two cubes, however, do not change in the same ratio as their linear dimensions, but rather with the square of the linear ratio. Similarly, the volumes of the cubes change in proportion to the third power of their linear dimensions. Say that the larger cube has a side twice as long as the smaller cube. Its surface area will then be  $2^2$ , or four times as large as the smaller cube, and its volume will be  $2^3$ , or eight times as great. The same rules apply to any other geometrically similar or isometric three-dimensional bodies, whatever the shapes. According to this rule, the size of a cross-sectional area of a three-dimensional object does not increase proportionally to the volume of this object, but only to the two-thirds power of the volume. With respect to our problem to relate CC cross-sectional area to FBV we can write out:

$$(i) \quad CC = \text{constant} \times \text{FBV}^{2/3}$$

This equation states that as FBV is increased the cross-sectional CC area does not increase in the same proportion, but only in proportion to the two-thirds power of FBV. Another fact which is related to that rule is that smaller bodies have, relative to their volumes, larger surface areas than larger bodies of the same shape. With respect to our problem, this can be expressed by dividing equation (i) by FBV:

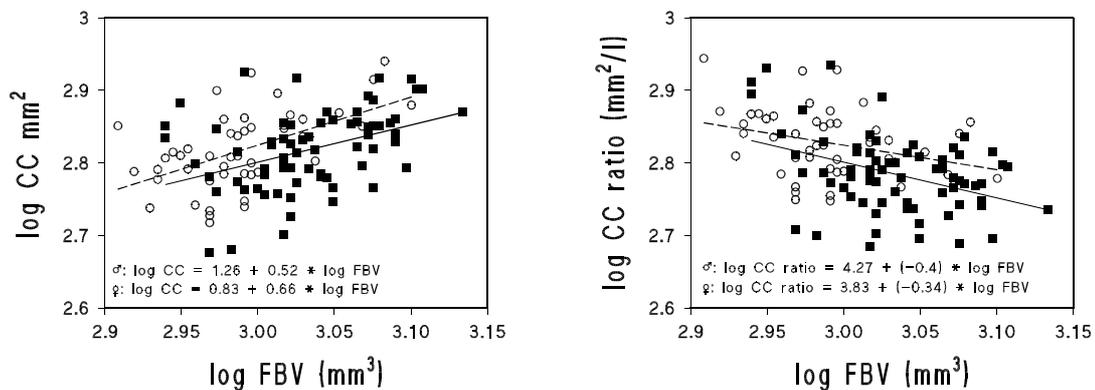
$$(ii) \quad CC/\text{FBV} = \text{constant} * \text{FBV}^{2/3}/\text{FBV}$$

$$CC/FBV = \text{constant} * FBV^{-1/3}$$

These equations can be transformed logarithmically revealing the following equations which are much easier to handle with conventional statistical software:

- (iii)  $\log CC = \log \text{constant} + 2/3 * \log FBV$ , and  
 (iv)  $\log CC/FBV = \log \text{constant} + (-1/3) * \log FBV$ .

In order to test whether the CC/FBV relation followed the geometrical rule we calculated the equations (iii) and (iv) and compared the slopes of interest with the hypothetical slopes derived from the geometrical rule ( $2/3=0.67$  or  $-1/3= -0.33$ ). If a cross-sectional area/volume relationship follows the geometrical rule the slopes are 0.67 in equation (iii), and -0.33 in equations (iv). In this case smaller brains have, relative to their volumes, larger cross-sectional CC areas than larger brains of the same shape.

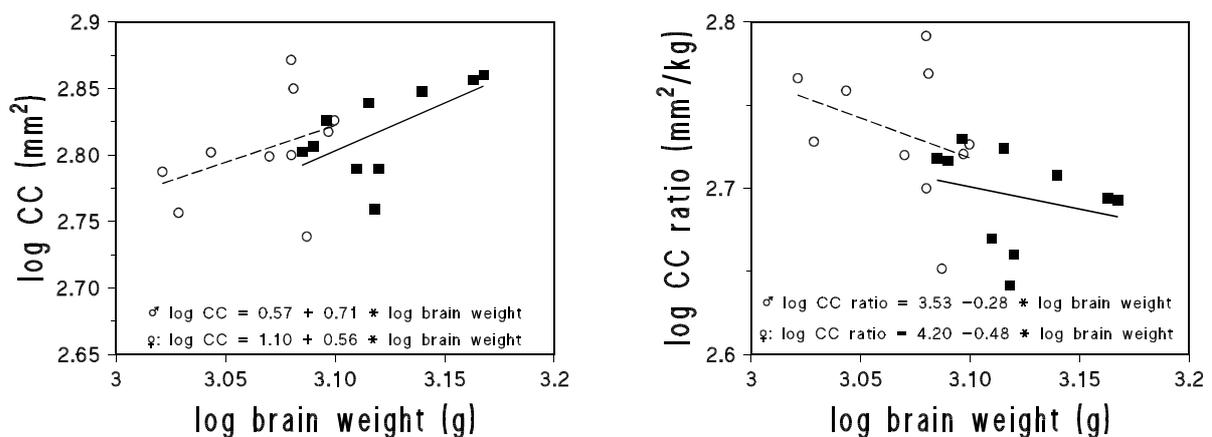


**Figure 1:** a) Total Corpus callosum (CC in log mm<sup>2</sup>) and forebrain volume (FBV in log l); b) Total Corpus callosum ratio (CC/FBV in log mm<sup>2</sup>/l) and forebrain volume (FBV in log l). Data are taken from (39). Unfilled circles indicate women, and filled squares men. Regression slopes for women are dashed.

On Figure 1a the cross-sectional CC area is plotted against the FBV on logarithmic coordinates. For this scattergram we obtained significant regressions (female:  $r^2=.30$ ; male:  $r^2=.17$ ) with slopes of 0.66 (females) and 0.52 (males). Both slopes significantly differed from 1 indicating that log CC area increases less than proportional to log FBV. More important, both slopes do not differ from 0.67 indicating that these relations followed the geometrical rule. If, instead, CC area per unit FBV (CC ratio) is plotted (Figure 1b), the regression line shows that the relative surface area decreases with increasing FBV. The slopes of these regression lines are -0.34 (females) and -0.48 (males). When total CC is divided into subareas (anterior third, middle third, isthmus, and splenium according to (73)), the relation between CC area measurements and FBV remains fairly stable. A further result of these analyses is that there are no substantial gender differences with respect to the CC/FBV relationships. Thus, the geometrical rule is appropriate to describe the CC/FBV relationship for both genders not only for the total CC but also for CC subareas (for details see (39)).

In order to cross-validate our results we reviewed the literature for those studies giving total CC size and precise brain size measures. We only found studies relying on postmortem analyzed

brains (3,8,18-20,30,48,69,73,78). From these studies mean CC area size<sup>2</sup> as well as mean brain weight were derived and plotted on<sup>3</sup> logarithmic coordinates. For this scattergram (Figure 2a) we obtained significant regressions (female:  $r^2=.16$ ; male:  $r^2=.42$ ) with slopes of 0.56 (females) and 0.71 (males). When CC ratios (CC/brainweight) are plotted as function of brain weight (Figure 2b), the regression line shows that the relative surface area decreases with increasing FBV. The slopes of these regression lines are -0.48 (females) and -0.28 (males). Thus, these analyses confirms our data. Taken together the data demonstrate that the CC/brain size relation follows the geometrical rule implying that the cross-sectional CC area increases less than proportional to brain size. It follows from this relationship that larger brains have relatively smaller cross-sectional callosal areas.



**Figure 2:** **a)** Total Corpus callosum (CC in log mm<sup>2</sup>) and brain weight (BW in gr); **b)** Total Corpus callosum ratio (CC/BW in log mm<sup>2</sup>/kg) and brain weight (BW in log gr). Data are taken from published postmortem studies (see text for further details). Unfilled circles indicate women, and filled squares men. Regression slopes for women are dashed.

Because cross-sectional CC area and callosal axon number are positively related in humans (2), our result suggests that the degree of interhemispheric connectedness may indeed decrease with an enlarging brain. This provides first empirical support of the aforementioned conjecture by Ringo et al. that brain size may be an important factor influencing interhemispheric communication (61).

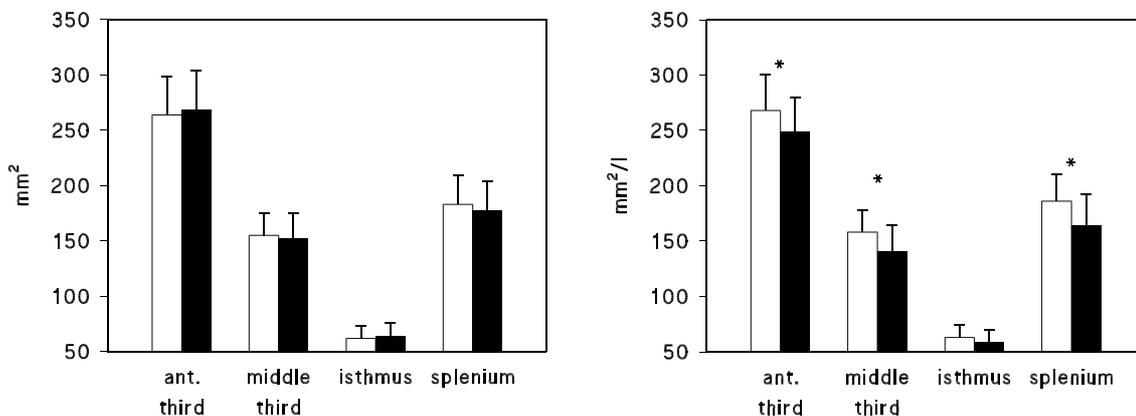
## Is there a true gender difference in the cross-sectional size of the corpus callosum?

Whether there are gender differences in the size or the shape of the CC is a long standing questions. The first author who evaluated gender differences in callosal area size was Bean (8) who found a larger genu in males. Shortly thereafter Mall (48), using a modern approach including a blind procedure (not used by Bean), failed to find differences in the CC that could be attributed to gender. This debate was reestablished by a postmortem study of De Lacoste-

<sup>2</sup> Because Weber and Weis only presented cerebrum weight we estimated total brain weight by adding hindbrain weight derived according to Blinkov and Glezer (10).

<sup>3</sup> De Lacoste and colleagues only presented brain weights of brains excluding the rhombencephalon. Therefore, brain weight was adjusted according to Blinkov and Glezer (10).

Utamsing and Holloway (19) who reported that women might have a wider and more bulbous splenium than men, and that even the overall size of the CC may be absolutely larger in women (30). The majority of follow-up studies failed to replicate these results (3,4,12,14,16,20,22,23,25-27,29,43,45,53,56-58,65,66,69,70). Nevertheless, most authors found a larger *relative* CC in women (i.e., CC relative to brain or skull size), or larger *relative* posterior portions of the CC in women (i.e., splenium or isthmus relative to total CC) (4,14,16,18,22,26,29,37,43,45,59,65,66,73). A typical result based on our previously described sample of 120 young and healthy subjects is shown on Figure 3a. This Figure illustrated that there is no gender difference in callosal size, neither for the total CC nor for the CC subareas (which are defined according to criteria suggested by Witelson (73) and Jäncke et al. (39). However, callosal size related to FBV revealed a stronger gender difference with women showing the largest CC ratios (Figure 3b). The common interpretation of this sexual dimorphism would be that it reflects increased interhemispheric connectivity due to increased female ambilaterality especially for temporoparietal cognitive functions (49).



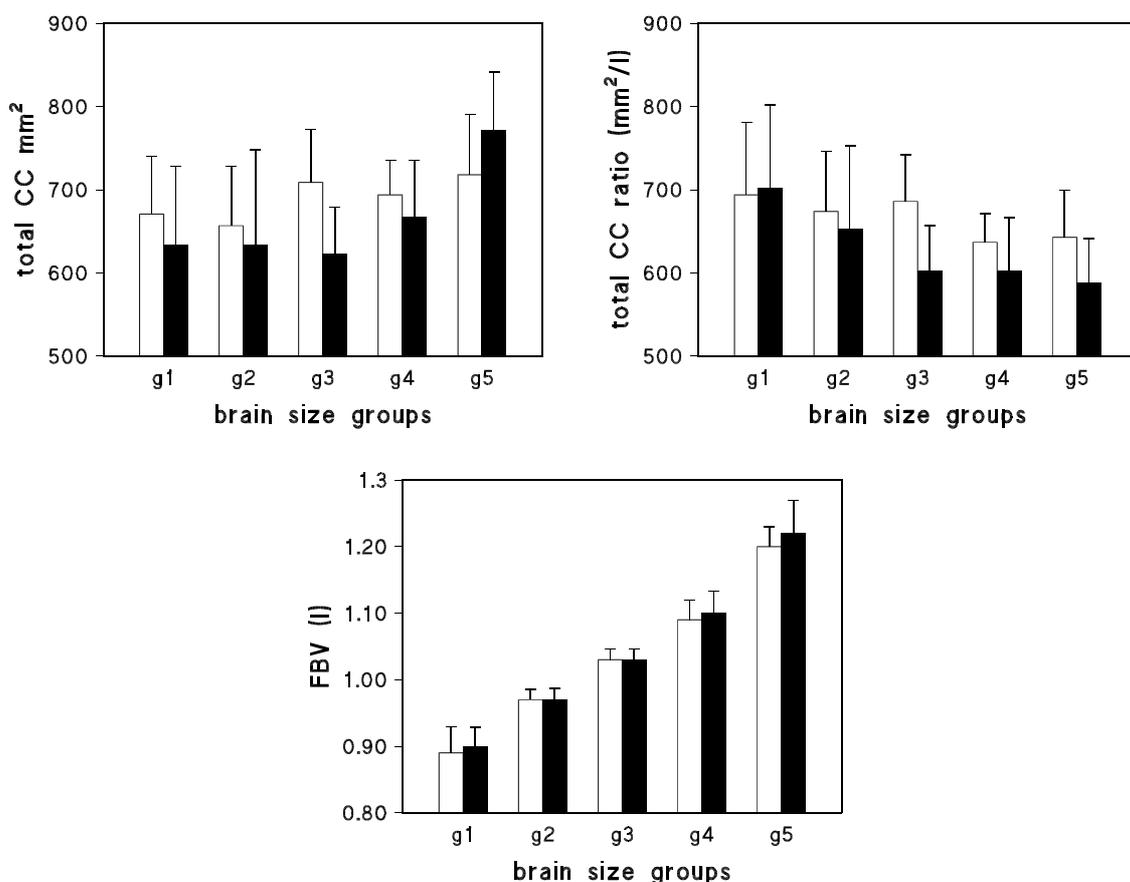
**Figure 3:** a) Mean CC subarea measures for women (□) and men (■). b) Mean CC ratios (CC subarea divided by FBV) for women (□) and men (■). Vertical lines indicate standard deviations.

In the light of the data presented in the preceding paragraph one might ask whether there is a true gender effect on relative CC area size or whether the relative CC size might be affected by a more general brain volume effect. In order to examine whether there was a true gender difference in the CC ratios (CC/FBV) we divided our sample into FBV quintiles, with 24 brains per quintile (Figure 4). For each FBV quintile t-tests were calculated to compare FBV and CC measurements between both genders. They revealed no significant gender differences, except for the third quintile comprising brains with FBV values of approximately 1.0 liter. For this group we found a larger total CC and CC ratio in women. Subsequent analyses revealed that this gender difference was restricted to the middle third and splenium. However, because this quintile comprised five female and 19 male brains, a sampling error is possible.

In our opinion these data suggest that brain volume is the main factor affecting relative callosal size. Because the CC/brain size relation follows a geometrical rule, larger brains will be associated with smaller CC ratios than smaller brains. Since on average women have smaller brains they will have larger CC ratios. More importantly, women with large brains do show small CC ratios while men with small brains show large CC ratios. Thus, the size of the CC and the CC ratio mainly depends on brain size and not on gender.

## Corpus callosum and brain lateralization

Witelson was the first to suggest that hand preference, interacting with gender, might also affect CC morphology (71,73-75). In her postmortem studies, non-consistently right-handed men showed larger total CC areas than consistently right-handed men or women. This suggested a relationship between laterality and callosal size, at least in men. Subsequent in-vivo imaging studies, however, revealed equivocal results. Whereas some investigators replicated the findings of Witelson and coworkers for absolute and relative CC subarea measurements (14,17,21,26), others could not confirm significant influences of handedness (39,45,50,52,59,65,66).

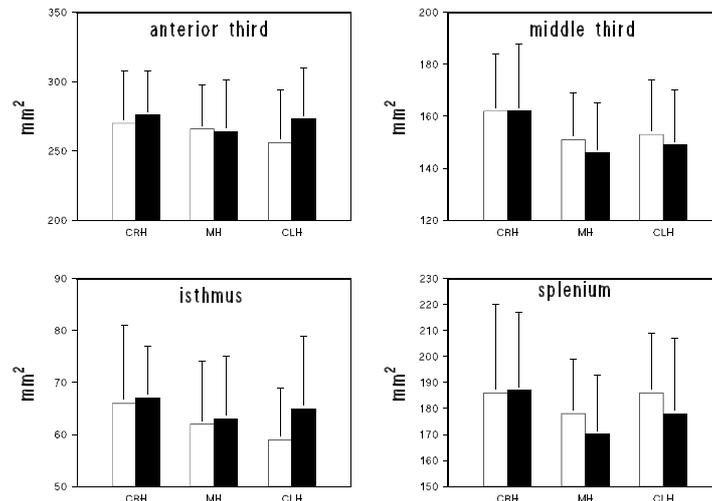


**Figure 4:** Mean total CC and CC ratios as a function of brain size groups (g1 to g5). Brain size in terms of FBV of the five brain size groups is depicted on the lower panel.

Further support that the CC is involved in the processing of lateralized functions comes from dichotic listening studies. Dichotic listening is a frequently used index of cerebral lateralization (11,31). The expected finding with verbal stimuli is a right ear advantage believed to result from left hemisphere lateralization of language function and greater efficiency of the contralateral auditory pathways in the simultaneous stimulation condition (46). It is thought that the CC may serve a critical function in transmitting verbal information from the left ear via the right hemisphere to the language areas on the left (46). This *callosal transfer model* has received support from studies on split-brain patients in whom complete left ear extinction has been observed. Sectioning of the anterior third of the CC, as well as sectioning of the splenium, is

consistent with intact left ear performance (24,62). The remaining critical sector is consistent with anatomical knowledge about the interhemispheric connections of the auditory cortices (64). It has been speculated that the anatomical variation in CC size or shape is of functional significance for cerebral lateralization (73). If behavioral measures of interhemispheric functions are related to morphometric measures of callosal connectivity, then left ear performance should correlate with CC size (because left ear stimuli are transmitted via the CC to the language areas in the left hemisphere). Laterality measures (e.g. right minus left ear performance) should correlate negatively with the size of the posterior body of the callosum (isthmus and splenium), where interhemispheric auditory fibers are presumed to be located in humans. This predicted structure-function relationship is based on the assumption that a larger callosal area is associated with more fibers and/or larger diameter fibers which, in turn, permit more efficient callosal transfer in this difficult task.

Witelson (72) was the first to test this hypothesis. She applied the dichotic listening test to 13 terminally ill male cancer patients whose brains were later analyzed in with regard to callosal morphology. She found that the size of the isthmus was negatively correlated with the difference between right and left ear accuracy of the dichotic listening task ( $r = -.55$ ). Five studies examining

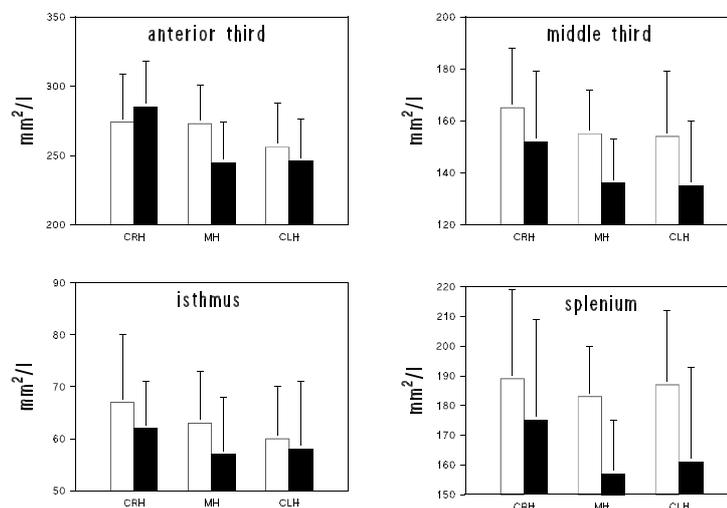


**Figure 5:** Mean CC subarea measures for consistent right-handers (CRH), consistent left-handers (CLH), and mixed-handers (MH) as a function of gender (women (○) and men (●)). Vertical lines indicate standard deviations.

callosum measures obtained from MRI and dichotic listening scores in normal subjects have produced equivocal findings. O’Kusky et al. (52) found significant negative correlations of a dichotic listening laterality index with total callosum area, as well as with two anterior callosum measures. Hines et al. (28) discovered a trend of a negative relationship between the size of the splenium and a laterality index in dichotic listening. Clarke et al. (15) found no correlations between left ear performance and size of the CC, but they did find a negative correlation between right ear score and size of the CC. They interpret their results as indicating an interhemispheric inhibitory-facilitatory function of callosal connections. Two further studies found no relation between midsagittal callosal measures and dichotic listening test results (40,45).

Because there have been only a few studies of the relation between behavioral laterality effects and callosum morphology there is a need for further investigation of this topic. We therefore examined the relationship between handedness and midsagittal corpus callosum area in our sample of 120 young and healthy subjects. We applied Annett handedness questionnaire (5) because this handedness classification has been validated with hand skill measures (37). As

shown on Figure 5 we discovered no substantial influence of handedness on CC size, neither for males nor for females. The same negative finding was found for callosal ratios (Figure 6). Thus, we could not confirm larger CC measurements in non-consistent right-handers, mixed-handers or consistent left-handers when compared to consistent right-handers. This is in agreement with the majority of studies investigating possible relationships between CC size and handedness (45,50,52,59,65). In our sample, consistent right-handers even showed a larger midbody than other handedness groups, which is in contrast to previous reports of opposite handedness effects (14,17,21,26,73). However, it should be mentioned that two of the latter studies (17,21) were reanalyzes of data for which a prior report (45) had failed to identify a gender or handedness difference, that the postmortem sample of Witelson (73) was relatively heterogeneous, and that the effect reported by Clarke and Zaidel (14) remained small. While our data may add further confusion to this part of the ongoing discussion, it appears fair to say that an influence of handedness on CC size or shape must remain questionable.



**Figure 6:** Mean CC ratios for consistent right-handers (CRH), consistent left-handers (CLH), and mixed-handers (MH) as a function of gender (women (○) and men (●)). Vertical lines indicate standard deviations.

Since handedness is only moderately related to brain asymmetry it is necessary to examine further behavioral laterality measures and their relation to callosum size. We therefore applied a consonant-vowel dichotic listening recall test (41) to young and healthy subjects (25 males and females) in whom the CC was measured using MRI. This sample was divided according to median-split into subjects with larger (16 men and 10 women) and smaller brains (16 women and 10 men). For each *brain size* group Pearson product-moment correlations were determined between the midsagittal CC subareas and (i) the dichotic listening recall scores for superior ear accuracy, (ii) inferior ear accuracy, and (iii) the dichotic listening ear difference scores. It should be reiterated here, that if behavioral measures of interhemispheric transfer functions are related to morphometric correlates of callosal connectivity, then inferior ear performance (left ear performance in right-handers and right ear performance in left-handers) should correlate positively, and laterality measures (e.g. superior minus inferior ear performance) should correlate negatively, with the size of the posterior part of the CC. As shown in Table 1, a different pattern of correlations between dichotic listening scores and CC size measures emerged for both brain

size groups. For subjects with large brains a pattern of correlations emerged which at least tentatively confirmed the predicted relation between interhemispheric functions and morphometric measures of callosal connectivity. We discovered moderate positive correlations between accuracy scores of the inferior ear and the size of posterior portions of the CC. In addition, there were negative (although not significant) correlations between the laterality measures and the morphometric CC measures. Thus, subjects who had larger posterior portions of the CC, tended to have better performance at reporting inferior ear items and tentatively demonstrated reduced behavioral laterality measures. For subjects with smaller brains we discovered positive correlations between the dichotic listening scores of the inferior ear and the size of anterior callosum measures, and positive correlations between the recall scores of the superior ear and posterior callosum measures. There were nonsignificant but positive correlations between the dichotic listening laterality score and CC subarea size for both groups.

**Table 1:** Correlation coefficients for 50 subjects divided according to brain volume into two groups (*large* and *small brain* group) between anatomical area measures of the corpus callosum and behavioral measures from a dichotic listening task. SE: superior ear report, IE: inferior ear report, SE-IE: laterality index.

	SE	IE	SE-IE
<b><i>large brains (n=25)</i></b>			
<b>anterior third</b>	+ .30	+ .30	- .12
<b>middle third</b>	+ .29	+ .45 *	- .14
<b>Isthmus</b>	+ .04	+ .38 *	- .24
<b>Splenium</b>	+ .19	+ .37 *	- .07
<b><i>small brains (n=25)</i></b>			
<b>anterior third</b>	+ .38	+ .45 *	+ .10
<b>middle third</b>	+ .55 *	+ .40 *	+ .26
<b>Isthmus</b>	+ .54 *	+ .33	+ .32
<b>Splenium</b>	+ .48 *	+ .22	+ .35

\*:  $p < 0.05$

These findings may be important in several ways: (i) They do not confirm the results of Clarke and Zaidel (15) and thus they mitigate the functional interpretation given by these authors that callosal size reflects an interhemispheric inhibitory-facilitatory function of callosal connections. (ii) Different patterns of anatomical-behavioral correlations emerged for the two brain size groups. While the pattern observed for subjects with large brains was in line with the predicted anatomical-behavioral relation, the correlations obtained for subjects with smaller brains did not follow this prediction. It might be possible that the fibers crossing the midline are involved in different interhemispheric functions depending on brain size.

However, one has to keep in mind that dichotic listening tests may not be a particularly reliable measure of lateralization or interhemispheric transfer. Ear asymmetry may also be influenced by factors unrelated to laterality, such as competitive attentional biases between the ears, individual differences in the capacity of ipsilateral auditory pathways, and variations in processing strategies (7,11,36). Thus, we cannot rule out that these factors might have attenuated relationships between dichotic listening scores and CC measurements in our study. Similarly, owing to the relative complexity of the tasks employed here, the dichotic listening test results may not only reflect interhemispheric transfer but intrahemispheric processing as well.

Our working hypothesis was based on the so called '*callosal transfer model*'. According to this model, only the dominant hemisphere processes auditory-verbal stimuli, so that laterality

effects are expected to reflect callosal transfer from the non-dominant to the dominant half of the brain. In contrast, the '*direct access model*' has suggested that the non-dominant hemisphere is also capable of processing auditory-verbal information, but less efficiently than the contralateral one (77). According to this model, dichotic listening results would reflect efficiency of information processing within each hemisphere.

In addition, one has to question whether midsagittal CC size is indeed a valid index of the conduction velocity of callosal axons. The study by Aboitiz et al. (2) demonstrated that CC subarea sizes are positively related only to the number of small-diameter (slow conducting) callosal fibres, but not to the number of large-diameter (fast conducting) axons crossing through. Unfortunately, we do not know which class of fibres is involved in the callosal transfer of auditory information as investigated here.

Nevertheless, the positive finding of our study was that the size of almost all CC subareas correlated with the dichotic listening accuracy scores (either for the superior or the inferior ear). In general, subjects with larger CC areas demonstrated better accuracy scores. Stimulus detection tasks have shown that recall and discrimination rates are very strongly associated with stimulus complexity and cognitive capacity (intelligence) (42). Interestingly, a previous study found evidence for a link between CC area size and verbal fluency, a further variable closely associated with cognitive capacity (28). Thus, it appears possible that precision and speed of cognition, essentials of intelligence, are somehow related to callosal size.

## Conclusion

A major aim of this presentation is to demonstrate that at least a part of the large interindividual variability in callosal size might be explained by brain size differences. Our analysis revealed that the CC/brain size relationship follows a geometrical rule implying that the cross-sectional CC area increases less than proportional than brain size (FBV or weight). It follows from this relationship that larger brains have relatively smaller cross-sectional CC areas. Nevertheless, this allometric relation with FBV still explained not more than 30% of the total variability in CC size observed in our sample, demonstrating that the thickness of the CC is still mainly influenced by other factors. The majority of callosal fibers are thought to originate from association cortices and subserve higher-order functions (1,33,47,54). Thus, as previously hypothesized by Peters (55), a possible lack of an allometric relationship between the size of the brain and the association cortices could account at least for some of the variation in CC size that remains unexplained by the CC/FBV relation.

Additional variance to CC morphology may be added by 'environmental' factors. In animal studies of postnatal development of the CC, the number of callosal axons in neonates exceeds that of young adults, suggesting that normal development involves the remodeling of axonal projections between the two hemispheres with a subsequent elimination of callosal axons (16,35,47). However, this reduction in the number of callosal axons, reflecting the selective elimination of axon collaterals or callosal neurons during the early postnatal period, can be manipulated experimentally by altering sensory or motor experience during early development (9,34). Studies of humans have suggested a considerable degree of callosal plasticity during brain development until adulthood possibly induced by environmental stimulation (4,57,63).

The lack of a principal gender difference in the CC/FBV relation implies that small brains exhibit larger CC ratios, irrespective of gender. Thus, FBV was the main factor explaining the gender difference in our sample of 120 young and healthy subjects. However, it has to be ruled out in future experiments whether gender might exert additional impact on CC morphology.

Based on present anatomical knowledge, a functional interpretation of this inverse relationship between forebrain size and relative callosal size must remain speculative. Let us assume that the packing densities and branching patterns of callosal neurons and axons do not depend on brain size. In this case our data would indicate that the degree of interhemispheric connectedness decreases with increasing human brain size. This would concur with theoretical predictions made by Ringo and coworkers (60,61). They argued that as brain size is scaled up there must be a fall in interhemispheric connectivity, due to the increasing time constraints of transcallosal conduction delay. Consequently, functionally related neuronal elements would cluster in one hemisphere, so that increasing brain size would be the driving force in the phylogeny of hemispheric specialization. With regard to callosal connectivity, our morphometric data provide first empirical support of this conjecture.

Our finding that CC size is related to FBV should motivate future studies to normalize CC measures to brain size measures, similar as it was originally proposed by (18). Brain size turns out to be an important variable in aging, psychopathology, and perhaps in cognitive capacity. Thus, it is necessary to rule out that subgroup differences in callosal morphology are not solely a function of brain size. Let us consider a study designed to compare CC size between mixed- and right-handers. The mean brain size of the mixed-handers might be slightly larger by sampling errors. Then it is most likely that the CC size measures of the mixed-handers are slightly larger than those of the right-handers. Therefore, it would be more appropriate to use brain size-normalized CC size measures or to compare handedness subgroups with similar brain size measures. In general, this problem can be extended to any study comparing CC size between subgroups, whether they are normal, dysphasic, autistic, schizophrenic, et cetera.

Previous *in vivo* MRI studies have tried to address this challenge by measuring total midsagittal cross-sectional area of both cerebral hemispheres to predict brain size (14,44,58). However, the postmortem study of De Lacoste and colleagues (18) demonstrated that such measures cannot be used to predict brain weight because the correlation between midsagittal surface area and brain weight is rather low ( $r=0.40$ ,  $r^2=.20$ ). Thus, it is necessary to measure brain volume more directly.

Our results supporting the conjecture that brain asymmetry might be linked to brain size may stimulate future intriguing research in a number of ways: An important question will be whether brains of different size differ in neuronal packing density and branching patterns of callosal axons. It will also be worth to examine the relationship between brain size, established behavioral (language lateralization) and structural asymmetries (e.g. planum temporale and planum parietale asymmetry, (38,67)). If there is indeed a relation between brain size and asymmetry, larger brains should demonstrate stronger anatomical and functional asymmetries. This then may even provide clues for the phylogeny of hemispheric dominance in the higher primates (61).

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