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The Brain Connection: The Corpus Callosum Is Larger in Left-Handers

Abstract. *The size of the midsagittal area of the human corpus callosum obtained from postmortem measurement varied with tested hand preference. The corpus callosum, the main fiber tract connecting the two cerebral hemispheres, was larger by about 0.75 square centimeter, or 11 percent, in left-handed and ambidextrous people than in those with consistent right-hand preference. The difference was present in both the anterior and posterior halves, but not in the region of the splenium itself. This callosal morphology, which varied with hand preference, may also be related to individual differences in the pattern of hemispheric functional specialization. The greater bihemispheric representation of cognitive functions in left- and mixed-handers may be associated with greater anatomical connection between the hemispheres. The naturally occurring regressive events in neurogenesis, such as neuronal cell death and axonal elimination, may be factors in the individual differences in brain morphology and in functional lateralization. Specifically, right-handers may be those with more extensive early elimination of neural components.*

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Functional specialization of the cerebral hemispheres in the mediation of cognition in humans has been known for over a century (*1*) and extensively documented (*2, 3*), but its neurobiological basis is not known. Right-left asymmetry in the pattern of cortical sulci and gyri, particularly in the posterior opercular regions, was documented long ago (*4, 5*). Only recently, however, has some quantitative study been made of gross anatomical (*6*) and histological (*7*) asymmetry, and has the anatomical asymmetry been suggested to be a substrate of functional asymmetry. It remains to be established whether these anatomical asymmetries have biological significance for hemispheric functional specialization (*8*). One of the main obstacles to such study is that information is difficult to obtain for both anatomical and functional asymmetry in the same subjects (*9*). A general pattern of hemispheric specialization, in which linguistic-sequential and spatial tasks are more accurately processed in the left and right hemispheres, respectively, exists for most people, but the pattern may vary in both direction and degree (*3*). Different patterns of lateralization may be associated with such factors as brain damage, extreme deprivation, cognitive disorders (*10*), sex, and, most clearly, hand preference (*3*).

Hand preference is related, although imperfectly, to the pattern of hemispheric specialization. Left-handers as a group have greater bihemispheric representation of cognitive functions than do right-handers (*3*). As the main interhemispheric tract, the corpus callosum plays an important role in hemispheric integration and possibly in hemispheric specialization. As part of a larger study on the relation of neuroanatomical and neuropsychological measures in the same subjects (*11*), it was possible to study the anatomy of the corpus callosum in relation to hand preference, which was chosen as an index of functional lateralization. Almost no data are available relating postmortem neuroanatomical measures to indices of functional lateralization (*12*).

I now report that the size of the corpus callosum is correlated with the neuropsychological measure, hand preference. The midsagittal area of the corpus callosum was larger in the left-handed and ambidextrous than in the right-handed by 73 mm^2, or 11 percent. Such a difference could represent as many as 25 million fibers (*13*). This finding may have implications for the neuroanatomical basis of hemispheric specialization and for the early neurobiological precursors of hand preference. The gross variation in callosal size makes it a potential morphological marker for use with new brain imaging technology such as magnetic resonance imaging (MRI) for the study of hemispheric specialization in vivo in normal humans and in clinical populations suspect for atypical functional lateralization.

The 42 subjects studied (*14*) ranged in age from 25 to 65 years at the time of death. The handedness test, adapted from a questionnaire by Annett (*15*), required the subject to demonstrate hand preference on 12 unimanual tasks. Of the 42 subjects, 27 showed consistent right-hand preference and 15 showed mixed-hand preference, the latter group showing various combinations of right- and left-hand preferences (*16*). Consistent left-hand preference is rare, and no consistent left-handers were available in this sample. Clinical postmortem examinations were obtained and each whole brain was removed and immersion-fixed in buffered 10 percent Formalin (*17*). After fixation, the brain was bisected sagittally to expose the corpus callosum (*18*). On a photograph (Fig. 1), the line indicating the extent of the callosum was used to define anterior and posterior halves and a posterior fifth (*19*). The posterior fifth is roughly congruent with the splenium, which is difficult to define as it has no distinct anterior boundary. Total and partial area measurements of the callosum were made from tracings of the outline of the callosum from the photographs (at magnification ×1) of the midsagittal section (*20*).

The right-handers (mean ± standard error of the mean, 50.3 ± 1.8 years old) and mixed-handers (48.7 ± 2.3 years) did not differ significantly in mean age at death [$t(40) = 0.51$, $P = 0.61$], nor in whole brain weight [1314 ± 20.6 g versus 1328 ± 43.3 g, respectively; $t(40) = 0.34$, $P = 0.74$] (*21*). The mixed-handers had significantly larger total, anterior half, and posterior half areas than the right-handers (Fig. 2). In contrast, the region of the posterior fifth did not differ significantly between hand groups (*22*).

Table 1. Mean scores ± standard errors for callosal area measurements for the four hand-sex subgroups. Abbreviations: CRH, consistent right-handers; MH, mixed-handers.

Groups	n	Measure						
		Age (years)	Brain weight (g)	Hand score (*16*)	Callosum (mm^2)			
					Total area	Anterior half	Posterior half	Posterior fifth
Males								
CRH	7	47.9 ± 5.1	1442.5 ± 16.7	11.3 ± 0.4	672.1 ± 19.4	367.4 ± 18.7	304.6 ± 10.0	180.7 ± 6.3
MH	5	48.6 ± 5.2	1511.4 ± 50.1	5.0 ± 2.8	800.6 ± 53.9	423.2 ± 21.6	377.4 ± 33.7	202.4 ± 14.1
Females								
CRH	20	51.1 ± 1.8	1269.0 ± 18.5	11.4 ± 0.3	654.8 ± 17.5	345.1 ± 9.6	309.7 ± 9.5	172.4 ± 6.4
MH	10	48.8 ± 2.4	1236.8 ± 31.9	4.8 ± 1.9	697.1 ± 27.9	376.6 ± 20.0	320.5 ± 12.6	178.4 ± 9.7

Sex was examined as a factor in callosal size since the size of the human brain is sexually dimorphic. Absolute brain weight and volume are significantly larger in males by about 10 to 15 percent, although the sexes do not differ in brain weight relative to body height (*23*). Since the male brain is absolutely larger, at least some parts must be larger, possibly the corpus callosum. Moreover, an analysis of possible sex differences in callosal size was of interest, as de Lacoste-Utamsing and Holloway (*24*) reported that a group of females had a larger posterior fifth [$t(12) = 1.85$, $P = 0.08$], and no difference in total callosal area, although their brain weight was lower than that of males.

Two-way analyses of variance [hand (df = 1,38) by sex (df = 1,38)] were done for age, brain weight, and each callosal score (Table 1). The groups did not differ significantly in age (hand, $F = 0.20$; sex, $F = 0.40$). As expected, brain weight in males was significantly greater ($F = 51.8$; $P < 0.001$). Mixed-handers again showed significantly larger callosal areas for all measures except the posterior fifth ($F = 6.6, 5.8, 4.3, 1.4$; $P = 0.01, 0.02, 0.05, 0.24$, for total, anterior half, posterior half, and posterior fifth, respectively). Sex was not a significant factor for any area measure, although males had higher scores on all four measures ($F = 3.2, 3.5, 1.6, 2.3$; $P = 0.08, 0.07, 0.22, 0.14$, respectively). No hand-by-sex interactions were significant.

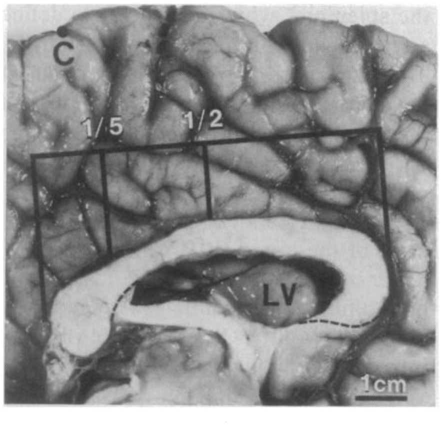

Fig. 1. The human corpus callosum is shown in midsagittal section with its boundaries indicated by dashed lines and with the subdivisions that were measured. The posterior end (splenium) is to the left. Abbreviations: C, central sulcus at the dorso-medial aspect; LV, lateral ventricle exposed by removal of septum pellucidum.

Since the sexes differed in brain weight and brain weight correlated with total callosal area ($r = 0.51$, df = 40, $P < 0.001$), covariate analyses were used to compare the sexes for callosal area relative to brain weight. A two-way analysis of covariance for hand by sex, with cerebrum weight (*25*) as the covariate, was done for each of the four callosal measures. The effect of hand was similar to the previous results ($F = 6.3, 5.7, 3.7, 1.1$; $P = 0.02, 0.02, 0.06, 0.31$, for total, anterior half, posterior half, and posterior fifth, respectively). Sex, again, was not a significant factor for any measure ($F = 0.7, 1.0, 0.2, 0.2$; $P = 0.40, 0.33, 0.65, 0.66$, respectively). The covariate was significant in each case beyond the 0.01 level. No hand-by-sex interactions were significant. The interaction factor for the posterior half measure had a probability level of 0.08. This result raises the possibility that the hand groups differ more in males than in females. The mixed-handers of each sex did not differ significantly in degree of left-hand preference [$t(13) = 0.14$, $P = 0.90$] (Table 1). Alternatively stated, there may be no sex difference in right-handers, but there may be in mixed-handers, with males tending to have a relatively larger posterior half.

In summary, mixed-handers were found to have a larger corpus callosum than consistent right-handers by about 11 percent. The difference between groups was not uniform throughout the callosum, being observed in the anterior and posterior halves, but not in the posterior fifth. In contrast to the hand factor, no sexual dimorphism in size of the callosum was observed. Males tended to have a larger callosum, but not significantly. In this sample of females, the posterior fifth was not larger as was reported by others (*24*), but on the contrary, tended to be smaller. When brain size was taken into account, there still were no sex differences. The values obtained in this study closely resemble those of an older extensive report by Bean in 1906 in which no sexual dimorphism was found in the posterior fifth of the callosum (*26*). The present results, however, do suggest the possibility of a complex sex factor which, in interaction with hand preference, may be related to the size of some segment of the posterior half of the callosum.

The magnitude of hand preference (*16*) did not correlate with callosal area for

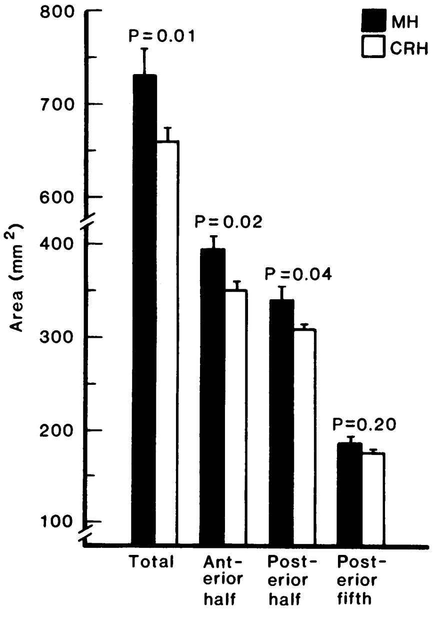

Fig. 2. Mean area measurements (± standard error of the mean) for the total, anterior half, posterior half, and posterior fifth of the corpus callosum for consistent right-handers (CRH) ($n = 27$) and for mixed-handers (MH) ($n = 15$). Each score is the mean of the right- and left-hemisphere measurements, and each hemisphere score is the mean of two measurements whose difference was less than 2 percent. Two-tailed t-tests (df = 40) were used.

the 15 mixed-handers, whose scores ranged from +10 to −6. The partial correlation between hand score and total callosal area, with cerebrum weight partialed out, was $r = -0.03$ (df = 12, $P = 0.92$); the partial correlation for absolute magnitude of hand preference was $r = 0.26$ (df = 12, $P = 0.40$). The classification of hand-preference groups has been a long-standing unresolved issue. The findings support the biological validity of a simple dichotomy, consistent right-handedness versus all others, a classification that is the basis of one theoretical model of the inheritance of hand preference (*16*). Such a model would predict that consistent left-handers, like mixed-handers, have a larger callosum than do consistent right-handers. To this end, MRI scans of the midsagittal section were obtained for two consistent left-handed men. Albeit measures from MRI scans and postmortem examinations are not perfectly comparable, for both men the total callosal area was greater than 3 standard deviations above the mean and greater than each individual score of the male right-handed group.

Since left-handers as a group show greater bihemispheric representation of cognitive functions, the difference in callosal anatomy between right- and mixed-handers may be associated with their different patterns of functional lateralization: specifically, the greater functional bilateralization may be associated with greater anatomical connectivity between the hemispheres (*27*). Implicit in this hypothesis is the notion that the gross anatomical difference reflects a functional histological difference. It remains to be determined whether the larger callosum of mixed-handers contains a greater total number of fibers, thicker axons, more myelin, or just fewer fibers per unit area. The human callosum is developed in shape and position early in fetal life, although it more than triples its overall size during postnatal development (*28*). Consequently, an experiential hypothesis might be suggested, that the greater bimanual experience of mixed-handers or the representation of language and of the sensori-motor functions of the dominant hand in opposite hemispheres, as exists in most left-handers, may result in the growth of more axons and a larger callosum. There is no evidence, however, to indicate that callosal axons grow across the midline at a time when such factors could have an effect.

Findings in developmental neurobiology offer an alternative interpretation. Naturally occurring regressive events, such as the death of neurons and the elimination of axon collaterals, play a major role in the final stages of neurogenesis, reducing the earlier overproduction of neurons and fibers (*29*). The callosum, like other fiber tracts, has markedly fewer fibers at maturity than in fetal and newborn stages, as has been shown in cats (*30*) and in humans (*31*). Elimination of callosal collaterals has been suggested to underlie this decrease in fiber number and to be completed soon after birth (*29, 30*). If more fibers do exist in the larger callosa of mixed-handers, the neuroanatomical difference between hand groups may be related at least in part to axonal elimination, which occurs prior to most environmental influences. Fewer fibers may be associated with fewer cortical neurons (*29*). Less gray matter was observed in right-handers than in left-handers, inferred from perfusion and clearance rates in regional cerebral blood flow studies (*32*).

In this neurobiological framework, variation in the mechanisms or in the extent of the regressive events in neurogenesis may result in different morphological modification of the callosum from an earlier undifferentiated state of fiber exuberancy. The more fruitful question may be not what leads to more fibers in non–right-handers, but what results in fewer fibers in consistent right-handers. The majority of individuals who are the consistent right-handers with marked hemispheric specialization may have fewer callosal fibers and a smaller callosum. In the minority of the population, about 35 percent, there may be less axonal elimination and larger callosa, and these may be the non–right-handers who have greater bihemispheric representation of function.

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17. To test for any effects of fixation, callosal measurements were made on several brains before fixation and after 4 months. No consistent shrinkage or expansion of the callosum was observed; J. M. van Buren and R. C. Borke [*Variations and Connections of the Human Thalamus* (Springer-Verlag, New York, 1972), vol. 1] have made similar observations on brain weight and volume.
18. The brain was bisected by retracting the hemispheres manually, allowing the insertion of a long knife with which the callosum was cut perpendicularly from anterior to posterior end, with the cut going through the septum pellucidum.
19. The callosum was subdivided a priori according to gross functional divisions based on topographical maps of the corpus callosum in relation to cortical connections in rhesus monkey [D. N. Pandya, E. A. Karol, D. Heilbronn, *Brain Res.* **32**, 31 (1971); B. Seltzer and D. N. Pandya, *Exp. Brain Res.* **49**, 147 (1983)].
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the mean absolute posterior fifth area for the group of nine males in the de Lacoste-Utamsing and Holloway (*24*) study were almost identical to those of this study; all the disparity stems from their group of five females whose posterior fifth ratio score was 0.31 and whose standard errors were large.

27. The results for the one left-handed subject who wrote with an inverted posture (subject 1) support the hypothesis of an association between callosal size and degree of hemispheric specialization. It has been suggested [J. Levy, *Psychol. Bull.* **91**, 589 (1982)] that inverted left-handed writers have greater functional bilateralization, at least for written language, than do left-handed writers with noninverted posture. The callosum of subject 1 was larger than that of any of the other four left-writing females, as well as being the largest of all 30 female subjects. One left-inverted male was available (one of the subjects who had magnetic resonance imaging). His callosal area was not only 5 standard deviations above the mean of the male right-handers, but was the largest of all the non–right-handed males.
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Genetics of Growth Predict Patterns of Brain-Size Evolution

Abstract. *Experimental evidence is presented supporting a developmental model that explains the genetic basis for brain and body size associations. Evolutionary change in body size causes correlated change in brain size because some genes affect both traits. The commonly observed correlation between brain and body size results from genetic variation in growth determinants affecting both traits simultaneously during fetal and early postnatal growth. Later growth reduces brain-body correlation because of changes in the underlying causal components of growth in each trait. Brain-body size evolution shows a different pattern at higher taxonomic levels from that seen within and between closely related species because body-size evolution among higher taxa occurs primarily by change in early portions of growth, which share more genetic growth determinants with brain size.*

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Perhaps the best-documented example of predictable developmental and evolutionary change is the scaling of brain size relative to body size in mammals (*1–5*). Here we report breeding experiments, with rats and mice, that reveal genetic relationships between growth of brain and body sizes. These genetic relationships help to explain commonly observed evolutionary patterns of relative brain size among mammalian species.

Brain size can be predicted by the allometric formula

$$\text{brain size} = a(\text{body size})^b$$

or

$$\log(\text{brain size}) = \log(a) + b \log(\text{body size})$$

where a and b are empirically fitted constants. The allometric coefficient b is the slope of a line in log-log scale. This slope varies among taxonomic levels (Fig. 1). Comparison of adults from different populations of the same or closely related species yields a slope of 0.2 to 0.4, but if adults of distantly related species are compared, a higher slope of up to 0.77 is found (*1–6*). There has so far been no satisfactory explanation for why allometric slopes are higher at higher taxonomic levels. We now present a simple causal model for the increase of brain-body allometric slopes with increased taxonomic level and provide experimental evidence supporting this genetic model.

One explanation for this relation of brain to body size among different taxa is that brain size changes as a side effect during body-size evolution (*1*). Adaptive change in body size occurs because natural selection changes the frequencies of genes affecting body size, some of which also affect brain size. This causes parallel change in brain and body sizes, depending upon the degree of shared genetic variation (pleiotropy). Parallel change in traits not directly selected for is ubiquitous in selection experiments (*7*) and has been demonstrated for brain and body size in rats and mice (*8*). The degree of pleiotropy can be judged from the genetic correlation between traits, as determined by selection or breeding experiments (*7*). The actual ratio of change in brain size per change in body size is predicted by the slope of the genetic regression of brain on body size (*6*). Quantitative genetic theory thus predicts the parallel response of two genetically correlated traits when one is subjected to selection.

When the two traits are logarithmically transformed to represent exponential relationships as linear, as in the allometric formulas presented above, the genetic regression of brain on body size defines an allometric slope along which populations will diverge when selected for different optimal body sizes (*1, 9*). Experiments with rats and mice (*8*) show that selection on body size will yield brain-body allometric slopes in the 0.2 to 0.4 range typical of slopes found when populations of the same or closely related species are compared (*1, 8*). This provides a simple, experimentally verified, genetic explanation of allometric slopes at these lower taxonomic levels: Evolution of body size causes parallel change in brain size because some of the genes that affect body size also affect brain size.

A likely source of genetic correlation between brain and body sizes is genetic variation in shared growth-regulating systems early in life, when both traits are growing rapidly. For example, embryonic somatomedin is a general mitogen affecting growth of many organs, including the brain (*10, 11*). If evolution of body size occurs by change in such systems, corresponding change in brain size is likely.

While this theory accounts for allometric slopes among closely related taxa, it does not explain why slopes are steeper among higher taxa. An equivalent change in body size causes a relatively larger change in brain size at higher taxonomic levels than it does among closely related populations. The question is then why the allometric slope increases, from around 0.4 to nearly 0.8, as we make comparisons higher up the taxonomic scale, going from species to genera, families, and orders (*12*).

A simple genetic explanation for this pattern of increased allometric slopes at higher taxonomic levels is now apparent. Body size can evolve either by change in the frequencies of genes that affect both brain and body size or by change only in the frequencies of those genes that affect