

Sexual dimorphism in interhemispheric relations: anatomical-behavioral convergence

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An embryogenetic hypothesis states that hemispheric specialization is inversely related to callosal connectivity (Geschwind and Galaburda, 1985). We tested this hypothesis (i) anatomically by relating postmortem planum temporale asymmetry to regional callosal morphology and (ii) behaviorally by relating the right visual field advantage in a lateralized lexical decision task with associative primes to regional callosal morphometry using magnetic resonance imaging (MRI). The postmortem study showed a significant negative correlation between planum temporale asymmetry and the number of small diameter fibers in the isthmus of the corpus callosum, but only for males. The MRI study showed a significant negative correlation between the right visual hemifield advantage for associated words and the cross section size of the isthmus of the corpus callosum, but again only in males. There was no sex difference in either the anatomical asymmetry, the behavioral asymmetry, or the callosal morphology. These convergent results suggest that there is a sexual dimorphism in interhemispheric relations in humans.

Key terms: anatomical-behavioral convergence, callosal connectivity, hemispheric specialization, interhemispheric relations, sexual dimorphism

INTRODUCTION

The prevailing view about sex differences in interhemispheric relations is that males are more lateralized and females are better connected between the hemispheres (*e.g.*, McGlone, 1980). This view can be interpreted both anatomically and behaviorally. Anatomically, we can look for sex differences in cortical asymmetries or in regional callosal size. Behaviorally, we can look for sex differences in behavioral laterality effects or in behavioral measures of interhemispheric transfer. Both interpretations are more complex than they may first appear. Anatomically, it is not clear which asymmetries should correspond to which functions. Similarly, the functional decomposition of the human corpus callosum is still largely un-

known. And how do we identify a greater anatomical connectivity through a putative callosal channel? Is larger simply better? Behaviorally, a significant behavioral laterality effect may reflect differences in hemispheric competence and/or in callosal transfer, depending on the task. And, again, it is not clear which callosal channels actually mediate interhemispheric transfer in a particular task. Much previous data on sex differences in interhemispheric relations fail to address these complexities or lead to conflicting findings.

Hemispheric independence and callosal channels

The anatomic model of behavioral laterality effects distinguishes three categories of

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tasks: (1) "callosal relay" tasks that are exclusively specialized to one hemisphere and require callosal relay of stimuli projected to the "wrong" hemisphere before processing can take place, (2) "direct access" tasks that can be processed independently, if differently, in either hemisphere, and (3) tasks that require interhemispheric interaction. Surprisingly many lateralized tasks are direct access, and one common index of hemispheric independence is a statistical interaction ("processing dissociation") between some independent stimulus variable (*e.g.*, Wordness [words, nonwords] in a lexical decision task) and visual hemifield of stimulus presentation (Zaidel, 1983; Zaidel *et al.*, 1990). Thus, predictions about the relationship of hemispheric specialization to callosal connectivity must refer to behavioral laterality effects in "direct access" tasks. Even so, such tasks can incorporate interhemispheric priming effects, resource sharing or other interactions that complicate the predictions (Iacoboni and Zaidel, 1995; Iacoboni, Rayman and Zaidel, Ms submitted).

Behavioral, anatomical and physiological evidence, both in clinical and in normal populations, now converge on the view that the human corpus callosum consists largely of a set of modality-, material-, or function-specific channels that interconnect homotopic cortical regions in the two cerebral hemispheres (Zaidel *et al.*, 1990). The anteroposterior arrangement of those channels respects the anteroposterior arrangement of the corresponding cortical regions: going in a caudal-rostral direction, the splenium interconnects visual cortices, the isthmus probably interconnects auditory cortices and superior temporal lobes, the posterior midbody interconnects somatosensory cortices, the anterior midbody interconnects motor cortices, and the genu may transfer control signals (including inhibitory ones) between frontal cortices.

Anatomy

Sexual dimorphism in the corpus callosum. What are the available data? Most of the published information concerns the splenium and the isthmus of the corpus callosum. De Lacoste and Holloway (1982)

first found a thicker splenium in females than in males. While three studies found a more bulbous splenium in females (Allen *et al.*, 1991; S Clarke *et al.*, 1989; Reinartz *et al.*, 1988), the majority of studies did not find significant sex differences in splenial measures (Byne *et al.*, 1988; Demeter *et al.*, 1988; Going and Dixson, 1990; Habib *et al.*, 1991; O'Kusky *et al.*, 1988; Oppenheim *et al.*, 1987; Prokop *et al.*, 1990; Steinmetz *et al.*, 1992; Weber and Weis, 1986; Witelson, 1989; Yoshi *et al.*, 1986). The normalized isthmus (corrected by total callosal area) was found to be larger in females than in males (Steinmetz *et al.*, 1992; Witelson, 1989), and the minimum body width, which is invariably in the isthmus, was similarly larger in females (Byne *et al.*, 1988). However, other researchers found no sex differences in the size of the isthmus (Allen *et al.*, 1991; Habib *et al.*, 1991; Oppenheim *et al.*, 1987) or even a larger isthmus in males (Denenberg *et al.*, 1991). All of these studies, whether post-mortem or in vivo magnetic resonance imaging (MRI), relied on morphometric measures of cross sectional areas of callosal regions, but none analyzed the number and type of callosal fibers. Thus, differences in corpus callosum size could reflect differences in the number of fibers, types of fibers or both. In the rat, sex differences in the size of the corpus callosum reflect differences in both number and type of callosal fibers (Juraska and Kopic, 1988). Whether similar relations exist in humans was unknown but is now addressed in the present experiment.

Sexual dimorphism in anatomical asymmetries. It is known that the human brain demonstrates anatomical asymmetries in regions related to Wernicke's area, particularly the Sylvian fissure and the planum temporale (Geschwind and Levitsky, 1968; Galaburda *et al.*, 1987). Furthermore, there is some evidence that these anatomical asymmetries are associated with the direction and degree of lateralization of language functions (Rattcliff *et al.*, 1980; Strauss *et al.*, 1985; Witelson and Kigar, 1988). There is also some evidence that anatomical asymmetries are larger in males (Wada *et al.*, 1975; McGlone, 1980; Kertesz *et al.*, 1987, 1992), although other reports indicate only minimal sex differences (Witelson and Kigar, 1992).

Behavior

Sex differences in callosal transfer. Potter and Graves (1988) used a variety of tasks to compare interhemispheric transfer between (left and right handed) males and females and found better visual transfer in females, and an interaction of sex and handedness in somesthetic transfer. But interpretations of those results are limited by the fact that the experiments contained only interhemispheric conditions with no intrahemispheric controls. Experiments in our laboratories have failed to find any systematic sex differences in interhemispheric functions. Clarke and Zaidel (1994) found no sex differences in visual or textural discrimination transfer. Clarke *et al* (1993), and Weekes *et al* (1995) used dichotic listening to nonsense syllables and neither found evidence for sex differences in callosal relay of the left ear signal (though both found involvement of sex with the laterality effect). Eviatar *et al* (1995) examined whether sex affects the bilateral distribution advantage in the Banich adaptation of the Posner-Mitchell letter comparison task (*i.e.*, faster comparisons between than within the hemispheres) and found a greater bilateral advantage in (right handed) males than females, suggesting that males have a greater flexibility of temporary functional disconnection supporting the bilateral advantage through parallel processing. Finally, Matteson (1991) teased apart the effects of sex and cognitive style in interhemispheric priming in a lateralized primed lexical decision task and found an effect of style but not of sex (Zaidel *et al*, 1995). Thus, there is no compelling evidence for greater functional callosal connectivity in females although few callosal channels, believed to be associated with these interhemispheric tasks, have been assessed systematically.

Sex differences in hemispheric competence. McGlone (1980) reviewed both pathological and normal data and concluded that left hemisphere specialization for language is greater in males than in females. But conflicting reviews showing no sex differences in behavioral laterality effects appeared subsequently (Fairweather, 1982; Hiscock *et al*, 1990, 1991; Voyer, 1994). Boles (1984) found no sex differences in

threshold word recognition experiments using accuracy as a dependent variable and hypothesized that sex differences in behavioral laterality effects are more likely to occur for speeded suprathreshold tasks that are sensitive to strategy shifts and use latency as a dependent variable. In turn, Healey *et al* (1985) believed that males are more lateralized in word recognition experiments with nonverbal responses, such as manual lexical decisions, whereas females are more lateralized in experiments that involve language production, such as naming. However, a review of some 30 lateralized lexical decision experiments in our lab revealed no consistent sex differences using either response measure (Zaidel *et al*, 1995). Similarly, a meta-analysis of a series of 10 lateralized tachistoscopic lexical decision and naming experiments showed that latency is not more likely to show sex differences, although lexical decision was more likely than naming to show greater lateralization in males.

The Geschwind-Galaburda hypothesis

A provocative hypothesis first articulated in Geschwind and Galaburda (1985) and elaborated in Galaburda, Rosen and Sherman (1990) argued that intrahemispheric and interhemispheric connectivities are inversely correlated and that both are related to anatomical and functional asymmetries. Thus, they purported to account for both intrahemispheric and interhemispheric sex differences in language organization. Specifically, greater asymmetry was said to be associated with decreased callosal connectivity and with a decrease in the size of the nondominant hemisphere, as well as with increased intrahemispheric connectivity. This suggestion is based on the negative correlations seen between the density and relative extent of callosal terminations and volumetric asymmetries in the somatomotor cortex of the rat (Rosen *et al*, 1989, 1990).

Galaburda *et al* (1990) proceeded to hypothesize that males (and left handers) have more symmetric brains, stronger interhemispheric connectivity and weaker intrahemispheric connectivity than females, so that they rely on bilateral language modules, whereas females rely more on LH modules.

They accounted for the smaller linguistic laterality effects in females by the facts that: (a) the female system, including the right hemisphere, is more efficient; (b) the female right hemisphere is less connected and hence less dependent on both callosal information and the left hemisphere; and (c) in females, the processing of left visual field (LVF) stimuli can be monitored more effectively using other well-connected modules in the right hemisphere.

Suffice to say that this unusual account seems to presuppose that there is better language competence in the right hemisphere of females than of males, that hemifield tachistoscopic testing operates largely by direct access, and that efficient linguistic processing in males is always dependent on interhemispheric exchange. Thus, this account blurs the distinction between direct access and callosal relay tasks. However, the hypothesis concerning the relation of anatomical and functional asymmetry to anatomical and functional callosal connectivity deserves further attention.

Callosal facilitation vs inhibition

Models of laterality effects which assume that the corpus callosum serves primarily excitatory functions (*e.g.*, Berlucchi, 1983; Sperry, 1962) versus primarily inhibitory functions (*e.g.*, Cook, 1984; Denenberg, 1983) lead to different predictions concerning the relationship between degrees of callosal connectivity and of behavioral laterality effects. The basic excitatory model posits that the corpus callosum serves to share information between the cerebral hemispheres. In this view, laterality effects should decrease with greater callosal connectivity since interhemispheric sharing of information would tend to mask underlying hemispheric differences in tasks that require interhemispheric exchange. Other laterality models argue for a role of the corpus callosum in maintaining independent processing in the two hemispheres (*e.g.*, Cook, 1984; Kinsbourne, 1982; Zaidel *et al*, 1990), such as the act of "shielding" the influences of one hemisphere from the other (Liederman, 1986). This latter view is compatible with an interhemispheric inhibitory role of the corpus

callosum. Here, laterality effects may be heightened by the presence of greater callosal connectivity, since interhemispheric inhibition would highlight the differences between the hemispheres. Physiologically, most, if not all, callosal fibers are excitatory in nature (Innocenti, 1986). However, inhibitory influences could be produced by post-callosal inhibitory interneurons. In sum, the inhibitory model predicts that laterality effects should be positively related to degree of callosal connectivity, while the excitatory model predicts a negative relationship in lateralized tasks that involve callosal transfer.

Evidence to date is scant and inconsistent, and has been primarily based on the dichotic listening task. Kertesz *et al* (1987) found no relationship between the laterality effect in dichotic listening to nonsense consonant-vowel (CV) syllables and total midsagittal callosal area. O'Kusky *et al* (1988) found a negative correlation between the laterality index in dichotic listening to words and both midsagittal callosal area and the area of the anterior callosum. Hines *et al* (1992) found a marginally significant negative correlation between the behavioral laterality index in dichotic listening to nonsense CV syllables and the combined area of the splenium and the isthmus. However, Clarke (1990) and Clarke *et al* (1993) used a dichotic nonsense CV syllables test whose interhemispheric structure had been analyzed in patients with complete cerebral commissurotomy and found a negative correlation between the *right ear score* and anterior callosal regions, consistent with the callosal inhibition hypothesis.

Organization of the paper

In the first experiment, we will explore post-mortem sex differences in planum temporale asymmetry, in regional callosal morphology and morphometry, and in the relation between them. We will focus on the isthmus of the corpus callosum which interconnects perisylvian cortex in the two hemispheres. In the second experiment, we will explore parallel sex differences in lateralized lexical decision, believed to be processed in superior posterior temporal cortex, and in regional MRI callosal morphometry, and in the

relation between them. In this way we focus on behaviors and anatomical structures and behaviors that are presumed to correspond to each other. In particular, we focus on a behavioral task believed to reflect relative, rather than absolute, hemispheric specialization, *i.e.*, hemispheric independence (direct access). Together, the two experiments provide convergent evidence for sexual dimorphism in the relation between hemispheric specialization for word recognition, presumed to be processed in perisylvian cortex, and callosal connectivity through the isthmus, which interconnects this specialized cortex.

The experiments are based on parts of the doctoral dissertations of Dr Francisco Aboitiz (1991) and Dr Jeffrey Clarke (1990), respectively, and some of the results are reported, together with other data, in Aboitiz *et al* (1992a, b, c) and in Clarke and Zaidel (1994). Some of these data have been presented in Zaidel *et al* (1995).

EXPERIMENT 1: POSTMORTEM ANATOMY

INTRODUCTION

In this section we discuss sex differences in the sizes of the left and right planum temporale and their asymmetry; in the sizes of different parts of the corpus callosum; in the fiber composition of these parts; and in the relationships among these asymmetries, the callosal morphometry, and the callosal morphology (Aboitiz *et al*, 1992a). The first question is whether gross callosal morphology reflects callosal microstructure, in terms of number and types of fibers in different parts of the corpus callosum. The second question is whether couplings between anatomical asymmetries in language areas and callosal macrostructure (by partition of a cross-section of the callosal area) are duplicated in parallel couplings between anatomical asymmetries and callosal microstructure.

METHODS

Aboitiz (1991) studied 40 human brains (20 females, 20 males), of people aged 25 to 60

years old who died from nonneurological causes, obtained from the Institute of Pathology, Hospital San Juan de Dios, Santiago, Chile. The mean age for the males was 48.5 years ($SD = 11.47$; range: 32-66) and the mean age for females was 45.1 years ($SD = 14.1$; range: 22-68). The brains were fixed in formalin and their surfaces photographed from their medial and lateral aspects. From these pictures, measures of the cross-sectional area of the corpus callosum as well as of the length of the Sylvian fissure in each hemisphere were obtained.

In this study, the length of the Sylvian fissure was calculated as the curved distance between the first gyrus of Heschl and the end of the superior branch of the Sylvian fissure (Aboitiz *et al*, 1992a). Heschl's gyrus was also measured to the end of the inferior branch, and to the branching point of the Sylvian fissure. However, these measures did not yield interesting relations and are consequently omitted. All these measurements were done using both a mechanical curvimeter and a computerized digitizing system. The linear depth of the planum temporale (called DPT), was calculated by a geometric approximation of the surface area of the planum (see Aboitiz *et al*, 1992a). The results were essentially similar to those obtained with Sylvian fissure measurements.

An absolute measure of asymmetry was used, defined as the magnitude of the difference between the left and right values (L-R), regardless of sign (that is, regardless of which side was larger). In addition, an asymmetry coefficient $(L-R)/(L+R)$ was determined, but as (L-R) did not correlate with (L+R), the coefficient did not yield results that differed from (L-R) alone.

The tracings of the corpora callosa were subdivided following Witelson (1989) according to straight length (see Aboitiz, 1992; Aboitiz *et al*, 1992a). The different callosal portions are, (1) anterior third (genu), (2) the area between the anterior third and middle of the callosal length (anterior mid-body), (3) the area between the middle of the callosal length and the posterior third (posterior mid-body), (4) the area between the beginning of the posterior third and the beginning of the posterior fifth (isthmus), and (5) the posterior fifth (splenium).

Additionally, the corpora callosa from a subsample of 20 brains (10 females, 10 males) were further processed for light microscopy study (Aboitiz *et al*, 1992b,c). Transverse sections at 5 μm intervals in the sagittal plane of the whole callosum were stained for myelin sheaths (Loyez procedure) and neurofibrils (Holmes procedure). From this microscopic material, the densities of fibers of different sizes were determined: larger than 0.4 μm , larger than 1 μm , larger than 3 μm , and larger than 5 μm in internal diameter. These counts were made in 54 x 54 μm fields across 11 regions in the corpus callosum (see Aboitiz, 1992; Aboitiz *et al*, 1992b, c). Measured diameters are estimated to shrink by 65% after the tissue is fixed and embedded in paraffin. Under the microscope, fibers were counted in three different areas at each locus (a counting area was defined by a reticle inserted in the microscope ocular). In each of these areas, two counts were always made, and the correlations between the pairs were high ($r > 0.9$). The standard deviations among the three different counting areas in each locus were usually below 5% of the mean.

RESULTS

Table I shows the means and standard deviations of the measurements of the Sylvian fissure (SF) in males and females. We did not detect significant side differences in the length of the Sylvian fissure, measured up to the end of its superior ramus. However, there were significant side effects when the depth of the planum temporale (DPT) was included in order to estimate the surface area of the planum temporale. Also, in agreement with Rubens *et al* (1976) and Witelson and Kigar (1992), the asymmetry levels of the measures ending in the inferior branch and in the bifurcating point were significant, favoring the left [$F(1,38) > 4.40$; $P < 0.05$; Aboitiz, 1991]. However, these measures did not yield interesting relations with other brain structures.

No significant sex differences were found in any measure of the Sylvian fissure, although on the average males had slightly larger measures than females. Likewise, the

proportion of individuals with rightward asymmetries was very similar in both sexes (Table I). The depth of the planum temporale (DPT) showed a significant sex difference [$F(1,38) = 6.51$, $P < 0.02$]. Planum area showed a tendency to be larger in males [$F(1,38) = 3.49$, $P < 0.07$]. No interaction was found between side and sex for any variable [$F(1,38) < 0.7$, $P > 0.4$].

Sylvian fissure length did not depend on brain weight in either males or females, nor did Sylvian fissure asymmetry (L-R) depend on total Sylvian fissure length (L+R). Finally, in both males and females, the Sylvian fissure asymmetry, regardless of its direction, correlated with the size of the right hemisphere rather than with the size of the left hemisphere, and the correlations did not differ significantly from each other. This pattern contrasts with that proposed by Galaburda *et al* (1987), who suggested that the smaller side determines the size of the asymmetry.

Callosum size

Although callosum size was about 6% larger in males, the difference was not significant.

TABLE I

Measurements of the Sylvian fissure

	Sylvian fissure length	Planum temporale depth
Males + Females (n = 40)		
Left	46.4 \pm 10.8	28.9 \pm 2.7
Right	42.9 \pm 11.4	27.9 \pm 3.3
Left > Right	(26)	(28)
Left < Right	(14)	(12)
Females (n = 20)		
Left	44.4 \pm 10.9	28.2 \pm 2.6
Right	41.3 \pm 13.5	26.7 \pm 3.7
Left > Right	(13)	(14)
Left < Right	(7)	(6)
Males (n = 20)		
Left	48.3 \pm 10.5	29.7 \pm 2.7
Right	44.5 \pm 8.8	29.0 \pm 2.4
Left > Right	(13)	(14)
Left < Right	(7)	(6)

Means \pm SD's, in mm. Number of subjects within parentheses.

Concerning specific callosal segments, the isthmus had the largest sex difference, favoring males [13%; $F(1,38) = 4.67$; $P < 0.05$]. No callosal segment was larger in females. These sex differences disappeared when measures were corrected for total callosum size or brain weight. Across all studies there was a positive correlation between callosum size and brain weight ($r(38) = 0.32$, $P < 0.05$), but this disappeared when the sexes were examined separately.

There was a significant correlation, only in males, between the size of the genu and brain weight ($r(18) = 0.49$, $P < 0.05$) that persisted when genu area was corrected for total callosum size ($r = 0.52$, $P < 0.05$). At the same time, in males, splenial area corrected for total callosum size showed a complementary negative correlation with brain weight ($r = -0.45$, $P < 0.05$).

Relation between Sylvian fissure length and regional callosum size

To determine a possible link between lateralization and interhemispheric connections, correlations were determined between asymmetries in the Sylvian fissure and the size of different callosal regions. When callosal measurements were correlated with the absolute values of Sylvian fissure asymmetries, a significant negative correlation was found between Sylvian fissure asymmetries and isthmus size (real value or normalized for total callosum size) in males only (females: $-0.17 > r > -0.24$, $P > 0.05$, $n = 20$; males: $-0.51 > r > -0.53$, $P < 0.05$, $n = 20$). The other callosum regions had near-zero correlations with asymmetries (Fig 1). Recall that these correlations were obtained only when using the Sylvian fissure measurement up to the end of the superior branch (see Aboitiz *et al*, 1992a).

The same relations were found when using planum temporale area estimations, although in this case significance levels rose to $P < 0.01$ (see Aboitiz *et al*, 1992a).

Fiber composition of the corpus callosum

Using the subsample of 20 brains, the total number of fibers of different sizes was calculated in each callosal segment and then

correlated with the magnitude of cerebral asymmetries (Aboitiz *et al*, 1989, 1992c).

The total callosal fibers estimated under light microscopy were (mean \pm SD) 160 million \pm 25 million fibers, a number slightly smaller than the 200 million reported by Tomasch some time ago (1954), using the same methodology. Electron microscopic examination of one corpus callosum revealed a low proportion of nonmyelinated fibers (less than 10%), and increased the estimate of total fibers to 177 million. Fiber density did not correlate with callosal area and hence an increased callosal area indicated more fibers crossing through, with the exception of the very large diameter fibers (larger than 3 and 5 μm , which constitute less than 0.2% of callosal fibers). These human findings contrast with results from monkeys, in which callosum size was found to be unrelated to the number of callosum fibers (La Mantia and Rakic, 1990).

We did not detect sex differences in callosal fiber composition or in numbers of fibers in any callosum segment.

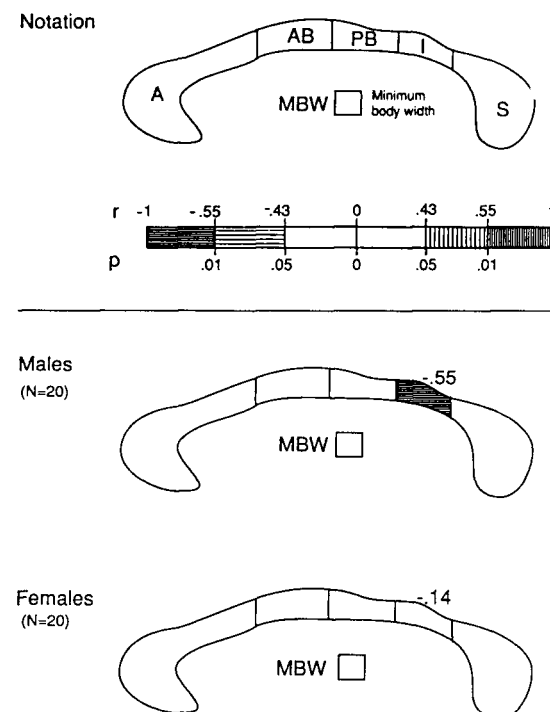


Fig 1. Experiment 1, postmortem study. Correlations between the absolute values of Sylvian fissure asymmetry and cross section areas of regions of the corpus callosum. A = anterior corpus callosum. AB = anterior body. PB = posterior body. I = isthmus. S = splenium.

Correlations between perisylvian asymmetries and fiber numbers

No correlation was obtained between Sylvian fissure asymmetries and the numbers of large fibers (larger than 3 and 5 μm) in any callosum segment, suggesting that these fibers do not tend to functionally interconnect those perisylvian areas.

Smaller diameter fibers had a relation to asymmetries that paralleled the morphometric findings. Figure 2 shows that in the isthmus of males only, asymmetries had a significant, negative correlation with the total number of fibers larger than 0.4 μm , and especially with fibers larger than 1 μm (but smaller than 3 μm). The sex difference in the correlation between Sylvian fissure asymmetry and Holmes count was significant. However, and not predicted by the morphometry, in females asymmetries correlated negatively with total fibers larger than 0.4 μm in the anterior splenium (Aboitiz, 1992; see Fig 2), which is adjacent to the isthmus.

(Note that the area of the splenium did not have a significant correlation with asymmetries.) Summarizing, in the isthmus of females and in the anterior splenium of males, the number of fibers smaller than 1 μm (about 80% of callosal fibers) correlated negatively with asymmetries. On the other hand, only in the isthmus of males did fibers larger than 1 μm but smaller than 3 μm (about 99.9% of callosal fibers) correlate negatively with asymmetries.

DISCUSSION

It seems that, in the posterior Sylvian fissure, the segments closer to Heschl's gyrus tend to be more asymmetric towards the left side, while if the superior ramus is included, the difference tends to disappear. However, when the area of the planum temporale is taken into account, the measure that includes the superior branch acquires a significant size asymmetry towards the left side. Al-

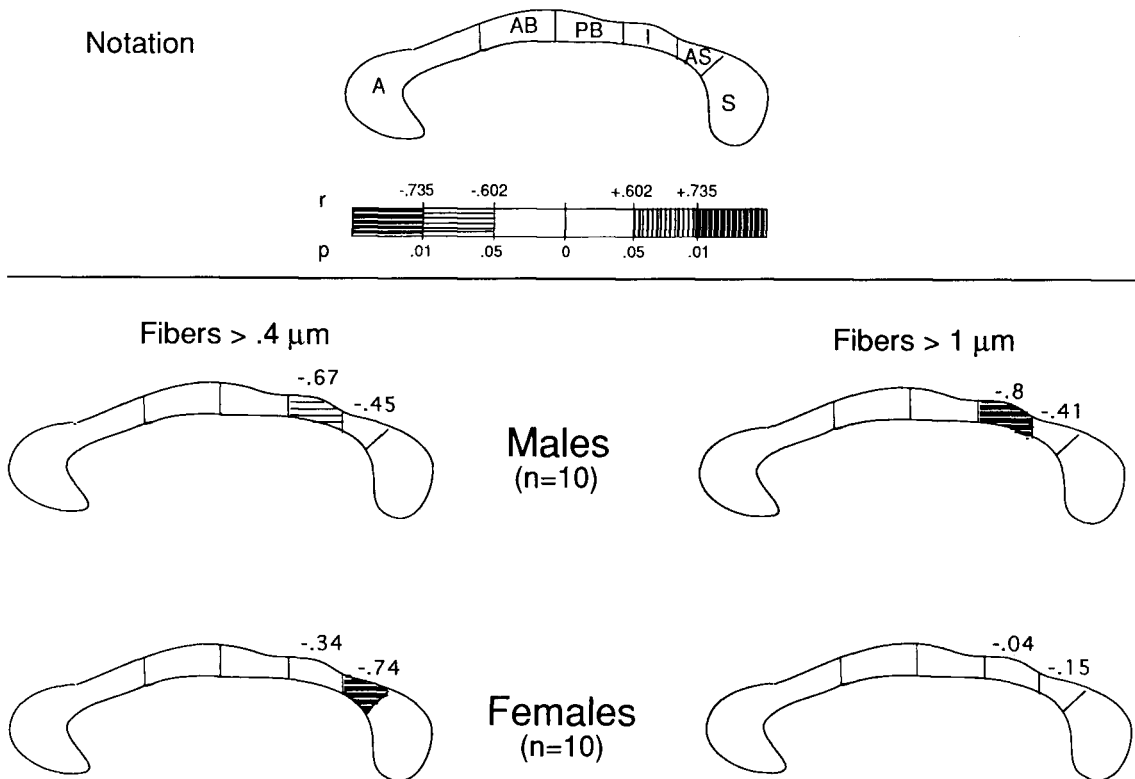


Fig 2. Experiment 1, postmortem study. Correlations between the absolute values of Sylvian fissure asymmetries and total fibers larger than 0.4 μm and larger than 1 μm in diameter (indicated in ten million fibers) in the callosal regions for males and for females.

though the superior branch did not yield significant asymmetry values, it was the only Sylvian fissure measure whose asymmetries has a significant correlation with callosal size and fibers. It is important to remember that a non-directional measure of asymmetries was used.

No significant sex differences in the Sylvian fissure were found, despite a robust sex difference in brain weight. This may be interpreted as due to the high variance of these measures. Note that Sylvian fissure length was independent of brain weight. We did not detect sex differences in the degree of asymmetries either. Witelson and Kigar (1992) obtained similar results in their sample. The only measure that indicated a sex effect was the depth of the planum temporale (DPT), and this may have been a consequence of its dependency on brain weight. These findings differ from Wada *et al* (1975) and McGlone (1980) who claim that males have larger anatomical asymmetries than females, and also from Geschwind and Galaburda (1985) and Galaburda *et al* (1990) who theorize that females should show larger anatomical asymmetries than males.

Witelson (1989) and Clarke (1990) found a sex difference in the isthmus in favor of females. In this sample, males had a larger isthmus than females, a difference that disappeared when correcting for brain size. Clarke (1990 and see Experiment 2 below) found that a measure of the minimal callosum width was larger in females. In the present experiment, the same analysis was made, resulting in a nonsignificant difference in favor of males. No sex differences in splenium size, even if corrected for total area (S Clarke *et al*, 1989) were found either.

In males, a correlation was found between the magnitude (not direction) of asymmetries in perisylvian areas and the size of the isthmus of the corpus callosum. This callosum region apparently includes fibers connecting those areas (De Lacoste *et al*, 1985; Pandya and Seltzer, 1986; Witelson, 1989).

No sex differences were found in the regional fiber composition of the corpus callosum. This result is interesting considering the robust difference in brain weight between the sexes. Peters (1988) argues that sex differences in brain weight relate to cortical

areas that receive and send projections to sensory and motor surfaces and not to association areas, which may comprise the bulk of the callosum projections. Hence, the lack of significant differences in callosal structure. Furthermore, it is still unclear whether the larger male brain (and presumably the larger cortex) includes a larger number of cortical cells. From cross-species comparisons, it is known that brain cell number increases at a slower rate than brain size (Jerison, 1973). Haug (1987) reported that cell density is smaller in the larger cortex of human males than in the smaller cortex of females, resulting in a similar number of total neurons in the two sexes. If this report turns out to be correct, it would not be surprising that there are no sex differences in callosum area, since similar numbers of neurons would project through the corpus callosum.

Aboitiz found a reduction in the number of callosum fibers as brain asymmetries increased, paralleling the morphometric studies. Overall, these findings agree with Rosen *et al* (1989), who found in the rat an inverse relation between volumetric asymmetries in the somatomotor cortex and the extent of callosal terminals connecting these regions.

The reduction of callosal connectivity with growing asymmetry may be explained in terms of a more extensive perinatal retraction of callosal terminals in asymmetric brains (see Galaburda *et al*, 1990). In the perinatal period of placental mammals, there is a dramatic retraction of the exuberant neonatal projections through the corpus callosum (Innocenti, 1986). It is believed that connections between different brain regions across the corpus callosum tend to be eliminated, among other things, by their lack of functional and topographic congruency with their synaptic counterparts (Aboitiz *et al*, 1992a, c). A more asymmetric brain would have more points of incongruency between the hemispheres than a more symmetric one, which would lead to a more dramatic retraction process.

Some recent reports propose that a smaller corpus callosum induces the process of hemispheric specialization during postnatal development (Lassonde *et al*, 1990; Witelson and Nowakowski, 1991). However, anatomical asymmetries are evident as early as the

seventh gestational month (Chi *et al*, 1977) or even before (Fontes, 1944), while the process of callosal fiber retraction occurs in the perinatal period (S Clarke *et al*, 1989). A likely possibility is that, after anatomical asymmetries have induced an increased retraction of axons in the callosum, the reduced corpus callosum itself plays a role enhancing the incipient lateralization, by constraining the communication between the hemispheres.

To summarize, although Aboitiz *et al* (1992b) did not detect sex differences in callosum fine structure, there were sex effects in the relations between fiber composition and anatomical asymmetries (Aboitiz *et al*, 1992c). First, the callosum regions that evidenced a negative correlation of total fibers with asymmetries were different for females and males: in females it was the anterior splenium while in males it was the isthmus (Figs 1 and 2). This finding may indicate (1) that a different topographic projection exists between perisylvian areas in the two sexes; (2) that different areas are asymmetric in females and males, even if in both cases this results in a similar difference in Sylvian fissure length; or (3) that both the isthmus and the anterior splenium include fibers connecting perisylvian areas in the two sexes, the difference resulting from a sampling error due to a limited number of subjects (10 of each sex). Further studies will help to elucidate this question. Meanwhile, one may tentatively conclude that there is greater interhemispheric cognitive (rather than sensory) independence and possibly greater intrahemispheric cognitive connectivity in males (*cf* Galaburda *et al*, 1990). Here, cognitive connectivity is determined by the number of small diameter fibers, which predominate between association cortices, whereas sensory connectivity is determined by large diameter fibers which predominate between sensory and motor cortices (Aboitiz *et al*, 1992b).

There is also the dramatic negative correlation of asymmetries with fibers larger than 1 μ m in the isthmus, seen only in males (Fig 2). The differences between the correlation values in the two sexes were significant in this case. Again, (1) it could be that these fibers do not connect perisylvian areas in

females, or (2) that the number of these fibers is insensitive to the development of asymmetries in females. In either case, the finding suggests that in males the relatively fast interhemispheric transfer of lateralized functions (*i.e.*, related to the larger fibers) will be especially reduced with increasing lateralization.

Perhaps, sexual dimorphism for higher cortical functions is established at a relatively late stage of embryogenesis when the absolute dimensions of anatomical structures are already determined but when their relative internal organization is still plastic. By analogy, it may follow that individual differences in higher cognitive functions reflect relatively late reciprocal rearrangements of neural structures.

EXPERIMENT 2: BEHAVIOR AND MRI

INTRODUCTION

This experiment seeks converging evidence from live subjects for the post-mortem data on the relationship between anatomical asymmetry and callosal connectivity. In this case, behavioral asymmetry on a lateralized lexical decision task takes the place of anatomical asymmetry in the planum temporale, and regional callosal morphometry takes the place of regional callosal fiber counts (Clarke and Zaidel, 1994). Based on the findings from the first experiment, we expect regional callosal morphometry to index cognitive callosal connectivity between association cortices in the two hemispheres rather than sensory/motor connectivity between primary sensory/motor cortices. Since in Experiment 1 we found a negative correlation between perisylvian asymmetry and the number of smaller diameter fibers in the posterior callosum, we would also expect a negative correlation between the behavioral laterality effect and posterior callosal morphometry in Experiment 2.

METHODS

Sixty UCLA graduate students received magnetic resonance imaging (0.3 tesla, TR =

500 msec, TE = 28 msec, slice thickness = 5 to 7 mm) and participated in a lateralized lexical decision task with semantic priming. Right-handed and left-handed males and females were equally represented (*i.e.*, 15 per group), and handedness was assessed using a modified version of the Edinburgh Handedness Inventory (Oldfield, 1971; Clarke and Zaidel, 1994). All subjects who wrote with their right hand were classified as consistent-right-handers, as each preferred to use his/her right hand for all nine of the hand preference items. Of the 30 subjects who preferred to use their left hand for writing, 14 were consistent-left-handers (*i.e.*, no right hand preference for any of the tasks) and 16 were mixed-handers (*i.e.*, right hand preference for at least one task). There were equal numbers of males and females in these two left-handed groups. Unless specified otherwise, the consistent-left-handers and the mixed-handers were treated as one group and will hereafter be referred to as left-handers.

Corpus callosum morphometry was assessed from tracings of the midsagittal view of the corpus callosum as seen by MRI. As there exists a topographical relationship between different corpus callosum regions and specific areas of the cerebral cortex (*e.g.*, De Lacoste *et al.*, 1985; Pandya and Seltzer, 1986), each corpus callosum was partitioned into five regions by dividing the maximum anterior-posterior corpus callosum length into halves, thirds, and the posterior fifth (as done in the first experiment). Consequently, as one moves from the posterior end towards the anterior end of the corpus callosum, one would expect to find localized interhemispheric functions related to, but not limited to visual perception, posterior language functions, audition, somesthesia, motor functions, anterior language functions, and executive functions associated with the prefrontal cortex. The maximum anterior-posterior length can either be defined by a straight line, or by a line that takes the curvature of the corpus callosum into account, both approaches were used (*cf* Clarke *et al.*, 1989; Witelson, 1989). The findings were the same for the two methods, and hence, we report the results from the straight-line methods, as this has been the more common approach used by researchers.

The primed lexical decision task is described in detail in Clarke and Zaidel (1994). Each trial began with a lateralized prime (a concrete noun) and was followed either by an English word (also a common concrete noun) or by an orthographically-regular nonword, which was also lateralized to the left visual field (LVF) or right visual field (RVF). Subjects were instructed to press a button if the second stimulus (*i.e.*, the target) was an English word. Three types of prime-target pairs were used: (1) associated prime-target pairs (*e.g.*, NEST - BIRD), (2) unassociated word pairs (*e.g.*, COAL - WEED), or (3) prime-nonword pairs (*e.g.*, SOAP - DERN). Each of these conditions were counterbalanced across all possible prime-target visual field combinations (*i.e.*, LVF prime - RVF target (LR), RL, LL, RR). Thus, both intrahemispheric (RR and LL) and interhemispheric (LR and RL) conditions were included. Each of the 128 trials consisted of the following sequence: 100 ms lateralized prime, 500 ms interstimulus interval, 60 ms lateralized target, and a 3 s period to respond if the target was a word (*i.e.*, Go/No go response), before commencement of the next trial. The response hand was alternated halfway through a session, and the initial response hand was counterbalanced across subjects.

RESULTS

Corpus callosum morphometry

Statistical analyses did not reveal any significant sex or handedness differences for either total midsagittal callosal area, or for the areas of any of the five subdivisions. We also considered the size of each callosum region normalized for total callosum area. In this case, normalized isthmus area (the region just anterior to the splenium or posterior fifth) was larger in females than in males [$F(1,56) = 4.81$; $P < 0.05$; $M = 8.70\%$ and 7.98% , respectively]. As the isthmus tends to form one of the narrowest parts of the callosum, we also measured the minimum width of this general area. Females had significantly larger isthmus widths than males, both in terms of non-normalized [$F(1,56) = 6.38$, $P < 0.025$; $M = 4.6$ and 4.0 mm, respectively] and normalized [$F(1,56) = 9.11$,

$P < 0.01$; $M = 17.7\%$ and 15.2% , respectively] measures.

There were no significant handedness differences in corpus callosum measures. In order to compare our results to previous studies, analyses of the data were repeated excluding the consistently left handed (CLH) subjects (*cf* Witelson, 1989; Habib *et al*, 1991). While no significant main effects of handedness were found, the sex by handedness interaction was significant for the normalized isthmus measure [$F(1,42) = 4.24$, $P < 0.05$] and approached significance for non-normalized isthmus area [$F(1,42) = 4.06$; $P = 0.0504$]. The isthmus constitutes a greater proportion of the corpus callosum in CRH females than in CRH males, while no sex difference is apparent for the MH group. More importantly, females showed no differences in normalized isthmus sizes for the two handedness groups, whereas a greater isthmus ratio for MH males than for CRH males approached significance ($P = 0.07$). To date, four different laboratories have shown isthmus measures to be invariable as a function of handedness for females, despite a handedness effect in males favoring those that are not CRH (Witelson, 1989; Habib *et al*, 1991; Denenberg *et al*, 1991; Clarke and Zaidel, 1994). A fifth laboratory found the isthmus to be proportionally larger in females than in males, although the sex by handedness interaction was not significant (Steinmetz *et al*, 1992).

Behavioral laterality effects

In order to examine effects of semantic relatedness, accuracies were determined for trials in which targets were English words. The independent variables were: sex, handedness, prime visual field, target visual field, and association (*i.e.*, whether a target word was semantically related or unrelated to the preceding prime word). The $2 \times 2 \times 2 \times 2 \times 2$ ANOVA did not reveal any significant effects involving prime visual field, so the data were re-analyzed collapsing across this variable. Two significant main effects were found, that of target visual field [$F(1,56) = 29.58$, $P < 0.0001$] and of association [$F(1,56) = 25.30$, $P < 0.0001$]. Accuracies were higher for RVF target presentations ($M = 81.4\%$ correct) than for LVF presentations

($M = 70.2\%$), and they were higher for associated prime-target pairs ($M = 79.7\%$) than for unassociated pairs ($M = 71.8\%$). The only significant interaction was that of handedness \times target visual field \times association [$F(1,56) = 6.22$, $P < 0.025$]. The simple interaction of target visual field \times association was significant for right-handers [$F(1,56) = 9.63$] but not for left-handers [$F(1,56) = 0.18$]. For right-handers, semantic facilitation (*i.e.*, the performance advantage of associated pairs over unassociated pairs) was greater for LVF target presentations than for RVF targets.

Anatomical-behavioral relationships

Pearson's product-moment correlation coefficients were determined, across all subjects, between each of the corpus callosum measures and the following behavioral measures from the lexical decision task: (1) overall accuracy, (2) accuracy for RVF targets, (3) accuracy for LVF targets, (4) a laterality index, lambda, which corrects for overall performance (where positive values reflect RVF advantages, negative values reflect LVF advantages; Bryden and Sprott, 1981), (5) absolute value of the laterality index (that reflects degree of laterality irrespective of direction), (6) accuracy for interhemispheric prime-target conditions (*i.e.*, RR and LL), and (7) the difference between the interhemispheric and intrahemispheric conditions (*i.e.*, a relative measure of interhemispheric advantage/disadvantage). For each correlation, significance was tested at the 0.01 level (2-tailed). None of these behavioral measures correlated significantly with any of the corpus callosum measures.

Additional anatomical-behavioral exploratory analyses were pursued that focused on correlations with isthmus size or minimum body width since (1) group differences were found for the isthmus and minimum body width, a finding shared by other studies (Byne *et al*, 1988; Witelson, 1989; Habib *et al*, 1991; Denenberg *et al*, 1991; Steinmetz *et al*, 1992), (2) the isthmus appears to be the callosal region containing the highest concentration of fibers from posterior language (*i.e.*, perisylvian) areas, and (3) isthmus measures have been shown to be related to anatomical hemispheric asymmetries in both

Sylvian fissure length and planum temporale area in males but not in females in the first experiment (Aboitiz *et al*, 1992a). Separate analyses for right-handers, left-handers, males, and females did not reveal any significant correlations ($P < 0.01$) between any of the above lexical decision measures and either isthmus size or minimum body width.

In the above analyses, the behavioral laterality index, lambda, included both associated and unassociated prime-target pairs. Since semantic relatedness affected performance, that, at least in the case of right-handers, interacted with target visual field, laterality indices were subsequently determined for associated and unassociated conditions separately. Isthmus and minimum body width measures were unrelated to the laterality index from the unassociated condition. When the laterality index from associated trials was considered, males showed significant negative correlations with both the normalized isthmus and the normalized minimum body width measures (Table II). In contrast to these negative correlations, the corresponding correlations for females were positive. This approached significance for normalized isthmus area ($r = 0.38, 0.05 > P > 0.01$) and was significant for normalized minimum body width ($r = 0.47, P < 0.01$) (Fig 3). However, the correlations for females were largely due to one subject with an outlying laterality score (nearly 3 standard deviations from the mean). When this subject was excluded, the correlations were not significant, but the differences between the correlations for males and females remained significant (Table II).

To determine whether or not such relationships were limited to the isthmus region, correlations were determined between the laterality index for associated pairs and all other callosum measures. No significant relationships were found ($P > 0.05$ in each case), suggesting that the laterality-callosal relationship is unique to the isthmus.

DISCUSSION

Individual differences in corpus callosum morphometry

Females had larger minimum body widths (actual and normalized measures) as well as

TABLE II

Correlation coefficients between behavioral laterality index and isthmus size

Correlation coefficients, for all subjects and for individual subgroups, between the laterality index from associated trials on the primed lexical decision task and the sizes of normalized isthmus area and of normalized minimum body width. Z-scores (Z) represent the difference in the correlations between males and females for each anatomical measure.

	N	Normalized Isthmus area	Minimum body width
All subjects	60	-0.05	-0.05
Right Handers	30	-0.04	-0.11
Left Handers	30	-0.09	-0.17
Males (M)	30	-0.52*	-0.48*
Females (F)	29#	0.18	0.38
Z (M-F)		2.76*	3.36**

* = $p < 0.01$; ** $p < 0.001$
 # = One subject excluded due to an outlying laterality score.

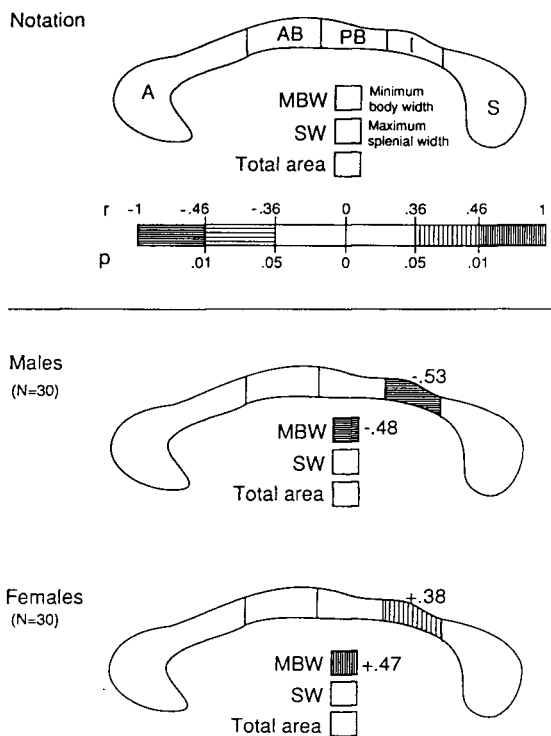


Fig 3. Experiment 2, MRI study. Correlations between the right visual advantage for associated target words and normalized cross section areas of regions of the corpus callosum.

larger normalized isthmus sizes compared to males. Larger minimum body widths in females had previously been reported (Byne *et al*, 1988). The minimum body width is invariably found within the isthmus, and the isthmus has been shown to be larger in females than in males when measured as percent of total corpus callosum area, but not when measured as actual area (Steinmetz *et al*, 1992; Witelson, 1989) which was found in the present study. Other studies have either found no significant sex difference in isthmus-related measures (Allen *et al*, 1991; Habib *et al*, 1991; Oppenheim *et al*, 1987) or an effect that favored males (Aboitiz *et al*, 1992a; Denenberg *et al*, 1991). However, except for Aboitiz *et al* (1992a), all other studies did not measure relative isthmus area in the same manner as Clarke (*i.e.*, Experiment 2), Steinmetz *et al* (1992) and Witelson (1989). In the Chilean sample reported by Aboitiz *et al* (experiment 1 above), actual isthmus area was larger in males than in females, while no sex difference was found for the normalized measure. Because the isthmus region appears to be the primary locus for fibers from posterior language areas, a sexual difference in isthmus morphology may be indicative of differences in hemispheric language organization between males and females (Witelson, 1989). Given this accumulating, although not conclusive, evidence for sex differences in the morphology of the posterior body of the corpus callosum, future studies should take a more refined approach to examining the morphometric parameters that best characterize this putative sex difference.

Although we did not find overall handedness effects, we did replicate previous findings of a sex by handedness interaction in the size of the isthmus when consistency of handedness was considered (Denenberg *et al*, 1991; Habib *et al*, 1991; Witelson, 1989). These three other studies had samples with either very few subjects who had consistent left hand preferences (Habib *et al*, 1991), or no such subjects at all (Denenberg *et al*, 1991; Witelson, 1989). In turn, Clarke (1990) found the sex by handedness effect for the isthmus only when consistent-right-handers and mixed handers were considered, excluding consistent-left-handers. The in-

termediate isthmus sizes of consistent-left-handers appeared to diminish the overall effect (however, see Steinmetz *et al*, 1992). As for the interaction itself, the common finding for all four studies (our own and the three others) is that males exhibit a handedness effect with isthmus measures being smaller in consistent-right-handed males than in mixed-handed males (this approached significance in the present study), while females do not show handedness differences in the isthmus. This finding parallels the finding in Experiment 1 that for males, but not females, isthmus area is smaller in individuals with greater anatomical hemispheric asymmetries of the planum temporale and Sylvian fissure.

We can speculate why the isthmus is associated with hemispheric asymmetries only in males. Sex differences in hormonal influences is a possible factor. Findings in the rat indicate that perinatal hormonal environment can have marked effects on the ontogeny of the corpus callosum (Fitch *et al*, 1991; Mack *et al*, 1993). Intrauterine hormonal influences may even contribute to individual differences in callosal development within a particular sex (Geschwind and Galaburda, 1985).

Isthmus size and semantic-verbal functions

Correlational findings from the primed lexical decision task provide compelling support for the view that for males, but not females, isthmus size is associated with cerebral hemispheric differences for posterior language functions. Those males with strong RVF advantages, indicating strong left hemisphere advantages, tended to have relatively small isthmus and minimum body width measures. It is interesting that these anatomical-behavioral relationships were only apparent for the lexical decision condition with semantic facilitation and not for other lateralized tasks (Clarke and Zaidel, 1994). Previous findings from right-handed split-brain patients as well as from normal subjects indicate that both cerebral hemispheres can make lexical decisions, although the left hemisphere is usually superior (Zaidel, 1983). Furthermore, the behavioral findings in right-handers suggest that the right hemisphere is particularly aided by semantic facilitation, consistent with previous findings

(Zaidel, 1983). In sum, isthmus size appears to be related to hemispheric differences in lexical functions in males under conditions in which the right hemisphere is 'performing' at its optimal level.

CONCLUSIONS

In Experiment 1, we found a negative correlation between Sylvian fissure asymmetry and the size of the isthmus in males only. Similarly, in Experiment 2 we found a negative correlation between a behavioral laterality effect and the size of the isthmus again in males only. This makes for converging behavioral-anatomical evidence for sexual dimorphism in interhemispheric relations.

The negative correlation observed in Experiment 2 between the (insignificant) right visual field advantage for associated targets in the primed lexical decision task and the size of the isthmus in males is very selective. There was no corresponding significant correlation between the isthmus and the (significant) right visual field advantage for unassociated word targets, nor for all word targets, nor for all targets (words and non-words). Further, there was no correlation with the isthmus for other visual, tactile and auditory behavioral laterality effects (Clarke and Zaidel, 1994). There was no correlation between the (significant) right ear advantage in dichotic listening and regional callosal morphometry whereas there were significant positive correlations between the (insignificant) behavioral laterality effects in visual shape and texture discrimination and the size of the midbody of the callosum (Clarke and Zaidel, 1994). All this argues against a general version of the ontogenetic callosal-elimination hypothesis of Galaburda *et al* (1990). Furthermore, a sex difference in a behavioral laterality effect appears to be independent of a sex difference in the corresponding callosal connectivity or in the relation between them.

Note that there was no correlation between performance on the interhemispheric component of the primed lexical decision task (primes and targets in opposite fields) and regional callosal morphometry. This supports

the conclusion that callosal size is not a reliable index of sensory transfer but rather of associative, functionally specialized connectivity.

In our proposed channel model of the corpus callosum, any region of the callosum contains multiple overlapping channels, both sensory and associative, facilitatory and inhibitory. Since the behavioral-anatomical correlations are significant for hemispheric models that maintain some strategy and resource independence, these correlations may not index real-time processing interactions but may reflect instead "off line control settings" involving facilitation or inhibition.

Taken together with other data (Clarke, 1990; Clarke and Zaidel, 1994; Zaidel *et al*, 1995), we see that sex differences in callosal anatomy, in behavioral laterality effects, and in cognition can all be independent of each other. In particular, sex differences in behavioral-anatomical correlations probably reflect sexually dimorphic development and mature functioning of high-level interhemispheric interactions. The data from the two experiments converge on the conclusion that there is sexual dimorphism in the relation of the asymmetry of perisylvian language gifted cortex and the corresponding channels of the callosum. Whether this sex difference can be extended to other asymmetric modules and their callosal channels remains to be explored.

ACKNOWLEDGMENTS

Thanks are due to Linda Capetillo-Cunliffe and Krista Schendel for assistance in preparing the manuscript. This work was supported by NIH grant NS20187 and by NIMH RSA MH00179.

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