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NUMBER 4

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THE HUMAN BRAIN EVOLVING:

Paleoneurological Studies in Honor of Ralph L. Holloway

Editors

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Florida Atlantic University

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FRONT COVER CAPTIONS

Center: Portrait of Ralph L. Holloway.
Upper left: A modern human brain.
Upper right: Ralph measuring landmarks on an endocast ca. 1976.
Lower right: Homo habilis cranium KNM-ER-1813 from Koobi Fora, Kenya (photo by Holloway).
Lower left: Ralph with an endocast of the Flores "hobbit" cranium.

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CHAPTER 14

SEX DIFFERENCES IN THE CORPUS CALLOSUM OF *MACACA FASCICULARIS* AND *PAN TROGLODYTES*

DOUGLAS C. BROADFIELD

ABSTRACT

In 1982 Ralph Holloway along with his student Kitty deLacoste-Utamsing published a paper asserting that there are sex differences in the brains of humans. While this was not the first paper on sex differences in the brain, it was one of the most prominent and controversial, setting off an area of neuroscience research that continues to today. While the extent and meaning of sexual dimorphism in the human corpus callosum has been investigated countless times over the past 30 years, what this structure is like in our closest relatives, the living apes, has not been approached. This paper investigates whether sex differences are present within two primate species, *Pan troglodytes* and *Macaca fascicularis*, addressing several issues important to neurology, paleoneurology, and human evolution. Looking at the morphological and histological aspects of these species demonstrates that there is not a statistically significant difference between males and females of *P. troglodytes* and *M. fascicularis* with regard to total and regional midsagittal area of the corpus callosum or with regard to axon density/100µm^2, overall axon numbers, or within any of the axonal diameter classes in the splenium of the corpus callosum in either species. These results strongly suggest that dimorphism of the brain and corpus callosum arose later in hominin evolution, possibly not until the arrival of *Homo sapiens*.

KEY WORDS

Brain evolution, corpus callosum, sex differences, chimpanzee, macaque

INTRODUCTION

The cerebral cortex has undergone a dramatic evolution during hominin history. Progressing from a small, chimpanzee-like brain in *Australopithecus*, and presumably *Ardipithecus*, the human brain has come to be capable of linguistic, mathematical, abstract, and behavioral elements apparently unobtainable by other primate groups. An additional aspect of this evolution has been the emergence of sex differences in cognitive behaviors. The existence of sex differences is not unheard of in primates (e.g., Philips et al., 2007), but it has been difficult to document in primate cognition (e.g, Hellner-Burris et al., 2010). Anatomical distinctions between nonhuman primates and modern humans have become more difficult as we have come to appreciate our evolutionary history. It is possible that during the course of primate evolution sex differences in the brain developed in early sexually dimorphic clades such as the cercopithecoids. This scenario is plausible due to the presence of sexually dimorphic skeletal morphology and group behaviors. Females behave differently from males, possibly due to different reproductive strategies. If sex differences occur in such phylogenetically distant taxa such as *Macaca* and *Papio*, it is possible that sex differences became even more distinct in a more recent common ancestor to humans such as *Pan*. The presence of sex differences in the brain of modern human's closest living relative would indicate that sex differences were already present in the earliest hominins. This would suggest that sex differences exhibited in modern humans are not unique, but merely an extension of *Homo*'s evolutionary past.

An alternative hypothesis suggests that sex differences in the modern human brain are unique to modern

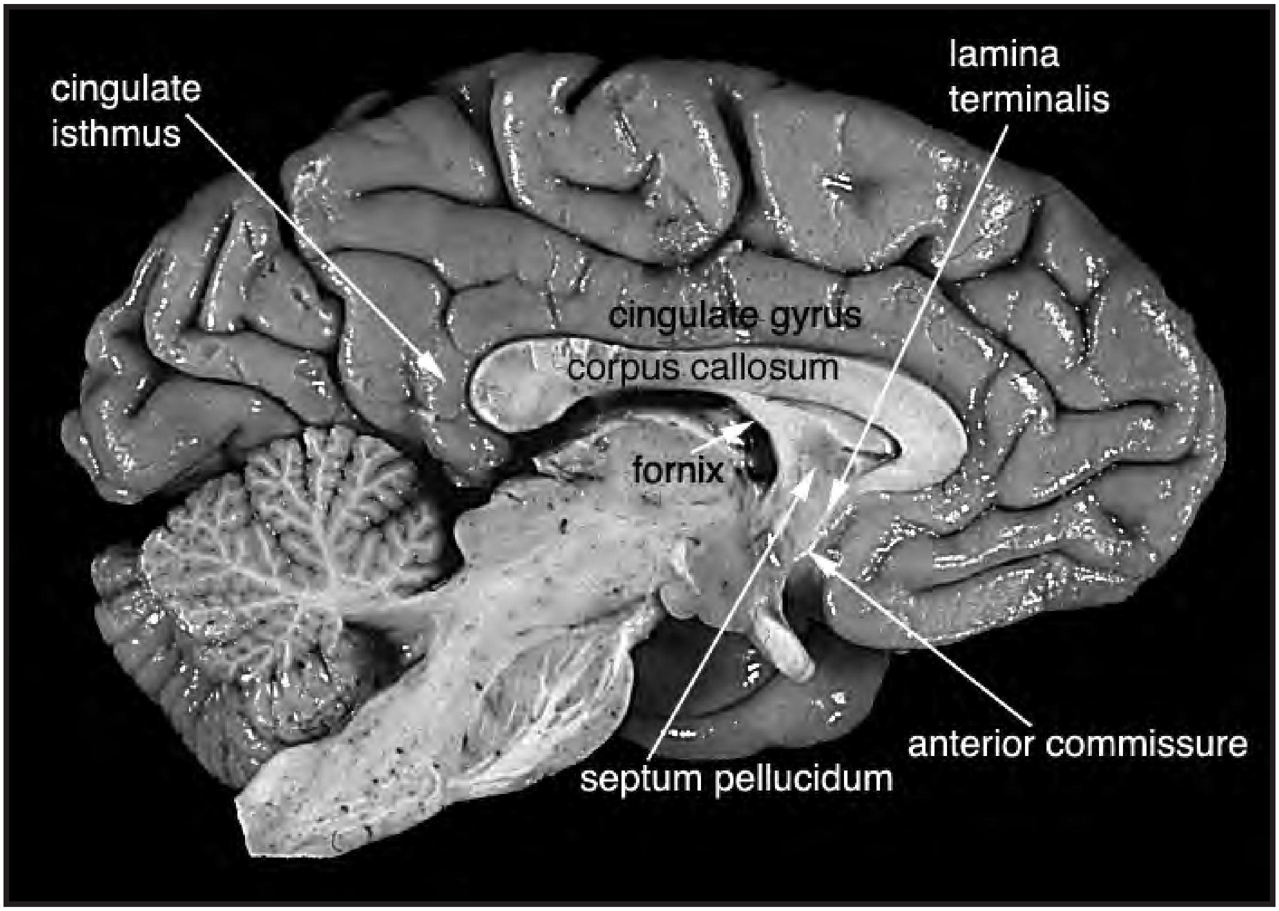

Fig. 1. Midsagittal view of brain of Pan troglodytes. A: anterior. P: posterior.

humans and did not occur until late in hominin evolution, possibly not until the advent of our own species, *Homo sapiens*. Although some similarity exists in the brains of *Pan* and modern humans, these similarities have not exposed any common sex differences between these two groups. Studies on modern human brains, however, have exposed a number of sex differences, albeit these discoveries occurred within non-neocortical structures. The presence of sex differences in cognition has also been observed. These results suggest that sex differences in the brain and in cognition did not occur until late in human evolution.

This study focuses on the second hypothesis that sex differences in the telencephalon occurred late in hominin evolution. The cerebral cortex represents one of the most complex and costly structures humans possess. The complexity of this structure has evolved over 3-5 million years of hominin history to allow modern humans to perform complex cognitive tasks not seen in other animal groups. In addition, humans have evolved the cerebral areas responsible for these tasks such that males excel at certain tasks while female excel at others. Males for example perform better at tasks of mental rotation while females do better on tests of verbal richness. There is little information about how these differences develop or within which specific cerebral structures they reside. One cerebral structure, however, has shed light on the presence of sex differences in the brain, the corpus callosum (Fig. 1). As the major interhemispheric pathway of the brain, the corpus callosum provides a point at which to begin to examine cerebral sex differences. Since morphological sex differences have been noted in this structure, the question of when these sex differences developed in human evolution can be asked. If the presence of sex differences in the corpus callosum represents an epiphenomenon of primate brain evolution associated with the advent of the Catarrhini, then sex differences in this structure should manifest in *Macaca*. If these differences don't occur until the evolution of the Hominoidea, then *Pan* would exhibit this trait. If sex differences in this structure did not occur until after the ape-human split, then it would represent an autapomorphic character of the hominin clade.

Considerable current controversy surrounds the existence of identifiable sexual differences in the nonhuman primate and human brain. An area that has come under increasingly greater focus is the corpus callosum, the principal neocortical commissure. For example, many recent studies on humans have demonstrated morphological differences between the sexes in callosal measures (de Lacoste-Utamsing and Holloway, 1982; Wium, 1984; de Lacoste et al., 1986; Holloway and de Lacoste, 1986; Holloway, 1990; Holloway et al., 1993; Davatzikos and Resnick, 1998; Oka et al., 1999; Sullivan et al., 2001; Allen et al., 2003; Lee et al., 2009) as well as fiber composition of the corpus callosum (Tomasch, 1954; Aboitiz et al., 1992a,b,c; Liu et al., 2010). Comparable data from nonhuman primates has, however, been generally lacking (e.g., Le May, 1976; de Lacoste and Woodward, 1988; LaMantia and Rakic, 1990a,b; Holloway and Heilbroner, 1991; Dunham and Hopkins, 2006; Phillips et al., 2007). The paucity of information on the primate corpus callosum has prevented further exploration of the origin, evolution, and functional significance of sex differences in the primate brain. Nevertheless, the limited information that is available for human and nonhuman primates provides provocative data concerning the above issues. In addition, the present study adds to the current knowledge of and provides new information on sex differences of this structure in *M. fascicularis* and *P. troglodytes*.

Sex differences in the corpus callosum of humans

The human corpus callosum has been the subject of extensive study relating to its involvement in a number of diseases such as: Down's syndrome (Wang et al., 1992; Kivitie-Kallio et al., 1998), epilepsy (e.g. Khanna et al., 1994; Hermann et al., 2003), amyotrophic lateral sclerosis (Yamauchi et al., 1995), Alzheimer's (Vermersch, 1996; Thompson et al., 1998), attention-deficit hyperactivity disorder (Baumgardner et al., 1996; Lyoo et al., 1996), autism (Piven et al., 1997; Manes et al., 1999), schizophrenia (e.g., Coger and Serafetinides, 1990; Raine et al., 1990; Hoff et al., 1994; Cowell et al., 1996; McCarley et al., 1999; Meisenzahl et al., 1999; Narr et al., 2000; Panizzon et al., 2003), Williams syndrome (Schmitt et al., 2001), Marchiafava-Bignami disease (Shiota et al., 1996), Tourette syndrome (Baumgardner et al., 1996; Mostofsky et al., 1999), dyslexia (Rumsey et al., 1996; Robichon and Habib, 1998) and other speech associated deficiencies seen when the corpus callosum is sectioned (Kaga et al., 1990; Davidson and Hugdahl, 1995). These studies, however, have done little to discern the sex differences associated with this structure.

Early studies on the corpus callosum found no differences in sex based on size and shape (Bean, 1906; Mall, 1909). However, subsequent research of this kind on the corpus callosum remained dormant until de Lacoste-Utamsing and Holloway (1982) re-addressed the issue. De Lacoste-Utamsing and Holloway took into account what Mall (1909) had stressed earlier, namely that brain size must be considered when suggesting dimorphism in brain morphology. They concluded that while the area differences between males and females may be small, they are nevertheless significant. Subsequent studies in this area have produced varying results. Some studies have suggested that there is sexual dimorphism in the corpus callosum (de Lacoste, 1981; de Lacoste-Utamsing and Holloway, 1982; Witelson, 1985; Holloway and de Lacoste, 1986; Yoshii et al., 1986; Reinarz et al., 1988; Clarke et al, 1989; Hayakawa et al., 1989; Witelson, 1989; Holloway, 1990; Elster et al., 1990; Allen et al., 1991; Clarke and Zaidel, 1994; Johnson et al., 1994, 1996; Driesen and Raz, 1995; Steinmetz et al., 1992, 1995, 1996; Salat et al., 1997; Davatzikos and Resnick, 1998; Oka et al., 1999; Achiron et al., 2001; Sullivan et al., 2001; Mitchell et al., 2003; Dubb et al., 2003; Westerhausen et al., 2004; Shin et al., 2005; Yokota et al., 2005; Lee et al., 2009). Others report that it lacks dimorphism (Bell and Variend, 1985; Weber and Weis, 1986; Kertesz et al., 1987; Oppenheim et al., 1987; Byne et al., 1988; Demeter et al., 1988; O'Kusky et al., 1988; Weis et al., 1989; Going and Dixson, 1990; Prokop et al., 1990; Denenberg et al., 1991a,b; Emory et al., 1991; Habib et al., 1991; Aboitiz et al., 1992c; Steinmetz et al., 1992; Zaidel et al., 1995; Constant and Ruther, 1996; Koshi et al., 1997; Matano and Nakano, 1998; Luders et al., 2003; Morton and Rafto, 2006). However, several of these latter studies did not consider sexual dimorphism in brain size, and thus did not analyze relative callosal measurements (i.e., taking brain size into account), but with the exception of Luders et al. (2003). Holloway et al. (1993) reexamined some of these results, and concluded that when brain size is taken into account sexual dimorphism in the corpus callosum is indeed indicated by such studies as: Witelson (1985), Weber and Weis (1986), Yoshii et al. (1986), Kertesz et al. (1987), Oppenheim et al. (1987), Byne et al. (1988), Demeter et al. (1988), Elster et al. (1990), Going and Dixson (1990), Habib et al. (1991), and Steinmetz et al. (1992).

In one meta-analysis, Bishop and Wahlsten (1997; see also Fitch and Denenberg, 1998) suggested that there are no sexual differences in callosal shape or size. It should be noted, though, that Bishop and Wahlsten downplay the effect of allometric scaling in the brain, proposing that it is not an appropriate way to analyze cortical data. This is contradicted by a more recent meta-analysis by Smith (2005), which demonstrated the importance of allometric considerations in comparative data, concluding that the corpus callosum of human females *is* relatively larger than that of males. Despite Smith's (2005) analysis there is still disagreement in the literature as to the validity of relative comparisons within species.

Reviews by McGlone (1980), Kimura (1980, 1983, 1987, 2000), Witelson (1983), Davidson and Hugdahl (1995), and Smith (2005) among others, confirm that there are sex differences in the brains of humans. Through cognitive studies on visuospatial tasks (see McGlone, 1980) and speech tasks such as speed of articulation, fluency within a language, and grammar (Hutt, 1972; LeDoux, 1982; Ross et al., 1997), it has been suggested that the adult male brain is more asymmetrical than the adult female brain with regard to verbal functions (Hutt, 1972; McGlone, 1977; LeDoux, 1982; Zaidel et al., 1995; Grimshaw, 1998), spatial functions (Witelson, 1977, 1983; Corsi-Cabrera et al., 1997), or both (Hutt, 1972; Springer and Deutsch, 1989). This information has led to the suggestion that the structure of the corpus callosum is responsible for certain sex differences in cerebral lateralization (de Lacoste-Utamsing and Holloway, 1982; Witelson and Kigar, 1987; Witelson, 1989; Holloway, 1990; Pulvermuller and Mohr, 1996; Funnell et al., 2000b).

Few studies have addressed the nature of the human corpus callosum on a histological level (Tomasch, 1954; Aboitiz et al., 1989, 1992b; Highley et al., 1999). Tomasch (1954) conducted the first study focused on the fiber composition of the corpus callosum. While he did not include any females in his study, Tomasch established the corpus callosum as the primary interhemispheric pathway. Later, Aboitiz et al. (1989, 1992a,b,c) reexamined the topic of fiber composition of the human corpus callosum. Unlike Tomasch (1954), Aboitiz et al. (1989, 1992a,b) included females in their sample. This allowed for a comparison of fiber numbers and types between sexes. From their examination of ten males and ten females they concluded that any differences in either total fiber number or fiber type were not statistically significant. While it was found that females posses more large myelinated fibers (> 3μm) than males, this difference was statistically insignificant. In addition, males were found to have more small myelinated fibers (< 3μm), yet this difference was also statistically insignificant. These results suggest that sex differences in the corpus callosum are not evident in the overall fiber composition of this structure. Although they do not specifically propose that sex differences in fiber composition may occur within certain callosal subsections, their data suggest that such differences may occur within certain regions such as the isthmus and midbody (Aboitiz et al., 1992a, 1996). While the above studies by Tomasch (1954) and Aboitiz et al., (1992a,b,c, 1996) have led to a greater understanding of the neuronal contribution to the corpus callosum, there is still a gap in studies on sexual differences that explain the cognitive differences seen between human males and females.

With regard to sex differences and pathology, Highly et al. (1999) found that there is a significant sex difference in the density of callosal fibers in normal and schizophrenic subjects. In the normal sample midsagittal area of the corpus callosum was not significantly different between males and females. However, normal females had a statistically significant greater density of callosal axons than males, especially in the splenium. The converse was found in schizophrenics. Male schizophrenics had a greater axon density in all callosal regions, especially in the splenium. A sex specific trend that occurs in schizophrenia is that along with a general reduction in brain size females exhibit a concordant reduction in fiber density in the corpus callosum, while males do not show a significant change. Why females show a dramatic reduction in the density of fibers passing through the corpus callosum, although the overall size of the corpus callosum, save the splenium, is not reduced from normal subjects, is difficult to discern. Highly et al. (1999) and Crow et al. (1998) conjecture that one variable that may account for the differences discussed above (i.e., the significant reduction in the size of the corpus callosum and fiber density in schizophrenic females) is the presence of increased lateralization or impairment of hemispheric communication in schizophrenia. Moreover, the significant difference in fiber density between normal males and females may explain certain cognitive differences between the sexes.

More recently, Westerhausen et al. (2003) did a study to see if gender is associated with microstructural differences in the human corpus callosum. They did find sex differences in the microarchitecture of the callosal pathways. This study was the first to find sex differences in the anisotropy of the corpus callosum (Westerhausen et al., 2003). Westerhausen et al. (2003) found a higher anisotropy value in the corpus callosum of the male subjects, which could result from fewer myelinated fibers and a lower density of fibers in the males. In a newer study by Westerhausen et al. (2004), the results were basically the same with the male subjects showing higher anisotropy than females and with higher anisotropy values in the posterior third as compared to the genu region. The males had a larger midsagittal area of the corpus callosum and a larger callosal area consisting of myelin than females (Westerhausen et al., 2004). In a recent study by Shin et al. (2005), they found decreased fractional anisotropy in the female corpus callosum as compared with that of the male, and conclude that the corpus callosum is a region of sex differences.

Sex differences in the corpus callosum of nonhuman primates and rodents

While studies such as Aboitiz et al. (1992a,b,c) and Highly et al. (1999) on humans have begun to address the question of the reality of gender-related differences in the corpus callosum, they have not completed the journey. Beginning with deLacoste-Utamsing and Holloway (1982), there have been many studies coming down on either side of the question. Obtaining an unambiguous answer is important, since the corpus callosum plays such an important role in lateralization of function in the brain, most importantly vision (Demeter et al., 1990; Payne, 1990; Krubitzer and Kaas, 1993; Vercelli and Innocenti, 1993; Intriligator et al., 2000) and speech (Kertesz et al., 1987; O'Kusky et al., 1988; Kaga et al., 1990; Galaburda, 1995; Preis et al., 2000). While all aspects of the human corpus callosum cannot be gleaned from studies on other mammals, examinations of this structure, however, in two particular mammalian groups, rodents and nonhuman primates, have provided clues about the function of the corpus callosum and its regions.

In response to the supposition of sex differences in the splenium of the corpus callosum in humans by de Lacoste and Holloway (1982), Juraska and Kopcik (1988) began to examine the development of sex differences in the corpus callosum of rats to determine the stimuli required to produce sex differences in this structure. In the first of a series of studies on the rat corpus callosum, Juraska and Kopcik (1988) found no sex differences in the size of the corpus callosum in rats that had either been raised in a complex environment or isolation, albeit they used only gross measurements. They did, however, find that females possessed more unmyelinated axons than males regardless of environment. In addition, females that were raised in a complex environment had more myelinated axons than similarly raised males, although males tended to have larger myelinated axons passing through the corpus callosum. The relevance of this study was to show that although morphological sex differences may not exist in the midsagittal area of the corpus callosum in humans, it is possible that axonal differences do exist. It also demonstrated that environmental conditions may influence the composition of this structure.

Subsequent studies on the corpus callosum have revealed sex differences in the fiber composition of the splenium. While there are no significant sex differences in the total number of axons passing through the splenium, there are sex differences in the types of axons in it. Females tend to possess more unmyelinated axons than males. In contrast, males possess larger myelinated axons than females (Kopcik et al., 1992; Mack et al., 1995; Kim et al., 1996). The production of the differences is currently a subject of debate. Are the differences merely environmental and thus developmental (Juraska and Kopcik, 1988; Kopcik et al., 1992; Kim and Juraska, 1997; Nuñez et al., 2000), or are they based purely on hormonal influences (Fitch et al., 1991; Mack et al., 1996; Bishop and Wahlsten, 1999; Bimonte et al., 2000)?

Many studies have focused on the sexual dimorphism of the human brain (Mall, 1909; Kimura, 1992; see McGlone, 1980; Falk, 1997 for reviews), but few have examined the issue in nonhuman primates (Le May, 1976; de Lacoste and Woodward, 1988; Falk et al., 1999; Franklin et al., 2000; Dunham and Hopkins, 2006; Phillips et al., 2007). At the same time most of the research that has been performed on sexual dimorphism in the brain of primates has had more to do with morphology than with the actual composition of this organ. The distribution of callosal fibers in nonhuman primates has been demonstrated several times (Seltzer and Pandya, 1983; Gould et al., 1986; O'Kusky et al., 1988; LaMantia and Rakic, 1990a,b; Beck and Kaas, 1994). Although LaMantia and Rakic (1990) approached gender differences in the course of their study, differences between the sexes with regard to fiber composition have yet to be sufficiently and specifically addressed.

De Lacoste and Woodward (1988) examined the midsagittal area of the corpus callosum in pongids, cercopithecoids, cebids, and strepsirhines. They found sex differences in the size of the corpus callosum and the width of the splenium relative to brain size in pongids. They also found sex differences in the size of the corpus callosum relative to brain size in strepsirhines. While these results would suggest that sex differences in the corpus callosum exist in certain primate groups, it should be noted that the four primate groups used in the above study (pongids, cercopithecoids, ceboids, and strepsirhines) are comprised of thirty-four species. Thus, their results are merely suggestive of sex differences in primate groups and not specific species. Other primate studies in which species were not combined show less sexual dimorphism in the corpus callosum than was previously suspected. Holloway and Heilbroner (1992) report that there are no sex differences in the corpus callosum or its subsections relative to brain size in *M. mulatta*, *M. fascicularis*, *Callithrix jacchus*, or *Saguinus oedipus*. Only *M. mulatta* demonstrated a slight sexual difference in the width of the splenium, with males being larger than females. Separately, Franklin et al. (2000) suggested that the total area of the corpus callosum is larger in *M. mulatta* males than females. They also showed that females possess a larger splenium. While these results are contrary to those of Holloway and Heilbroner (1992), it should be noted that the results of Franklin et al., (2000) are based on raw data and not relative measurements. Thus, these results merely serve to complicate the issue of sex differences in the corpus callosum. More recently, Phillips et al. (2007) demonstrated that female capuchin monkeys possess a larger corpus callosum compared to males with regard to overall size and posterior subregional measurements.

While the above studies have sought to determine sex differences in the corpus callosum of nonhuman primates based on total callosal area or subsectional areas, few studies have attempted to address the question of fiber differences in this important structure. Seltzer and Pandya (1983), Gould et al. (1986), O'Kusky et al. (1988), and Beck and Kaas (1994) have examined the topography of the nonhuman primate corpus callosum; however, these studies did not address the issue of sex differences. LaMantia and Rakic (1990a) also examined the development and topography of the nonhuman primate corpus callosum. In addition to their primary data, they also include anecdotal data on sex differences in the fiber composition of the corpus callosum in *M. mulatta*. In a comparison of two age- and brain weight-matched individuals, the male possessed 10 million more axons than the female, although the female's corpus callosum was larger. While this difference appears large, they suggest that the disparity could quickly disappear with a larger sample, since the corpus callosum normally contains fifty to sixty million axons in *M. mulatta*.

In general there is a paucity of data on sex differences in the corpus callosum of nonhuman primates. While the above studies have provided intriguing clues to the lack of definitive sex differences in this structure, the disparity of their results mandates the need for additional data, especially in species such as *Pan*. This includes information on the relative size of the corpus callosum in individual species as well as supplementary data on the fiber composition of this structure. Such data are important to understanding the function, development and evolution of human and nonhuman primate brains.

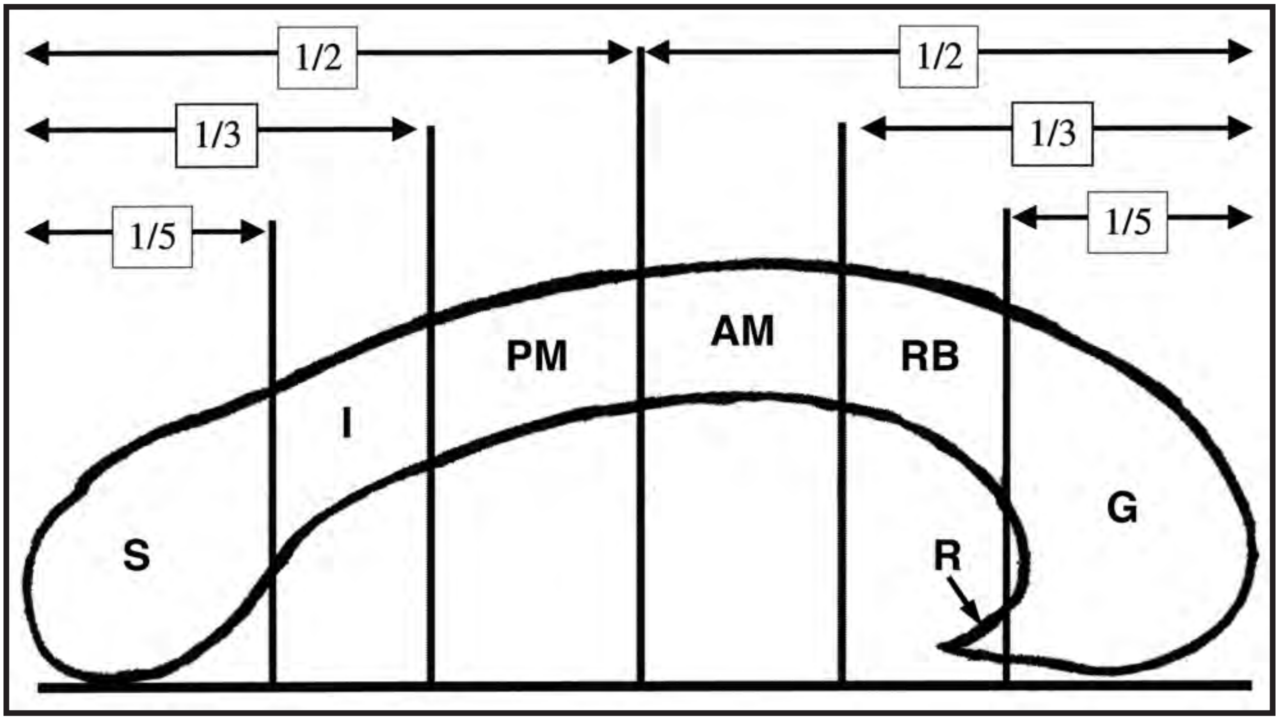

Fig. 2. Diagram of the midsagittal view of the corpus callosum of an adult human, showing the regional subdivisions. S: splenium, I: isthmus, PM: midbody, posterior midbody, AM: midbody, anterior midbody, RB: genu, rostral body, G: genu, R: rostrum. (after Witelson, 1989)

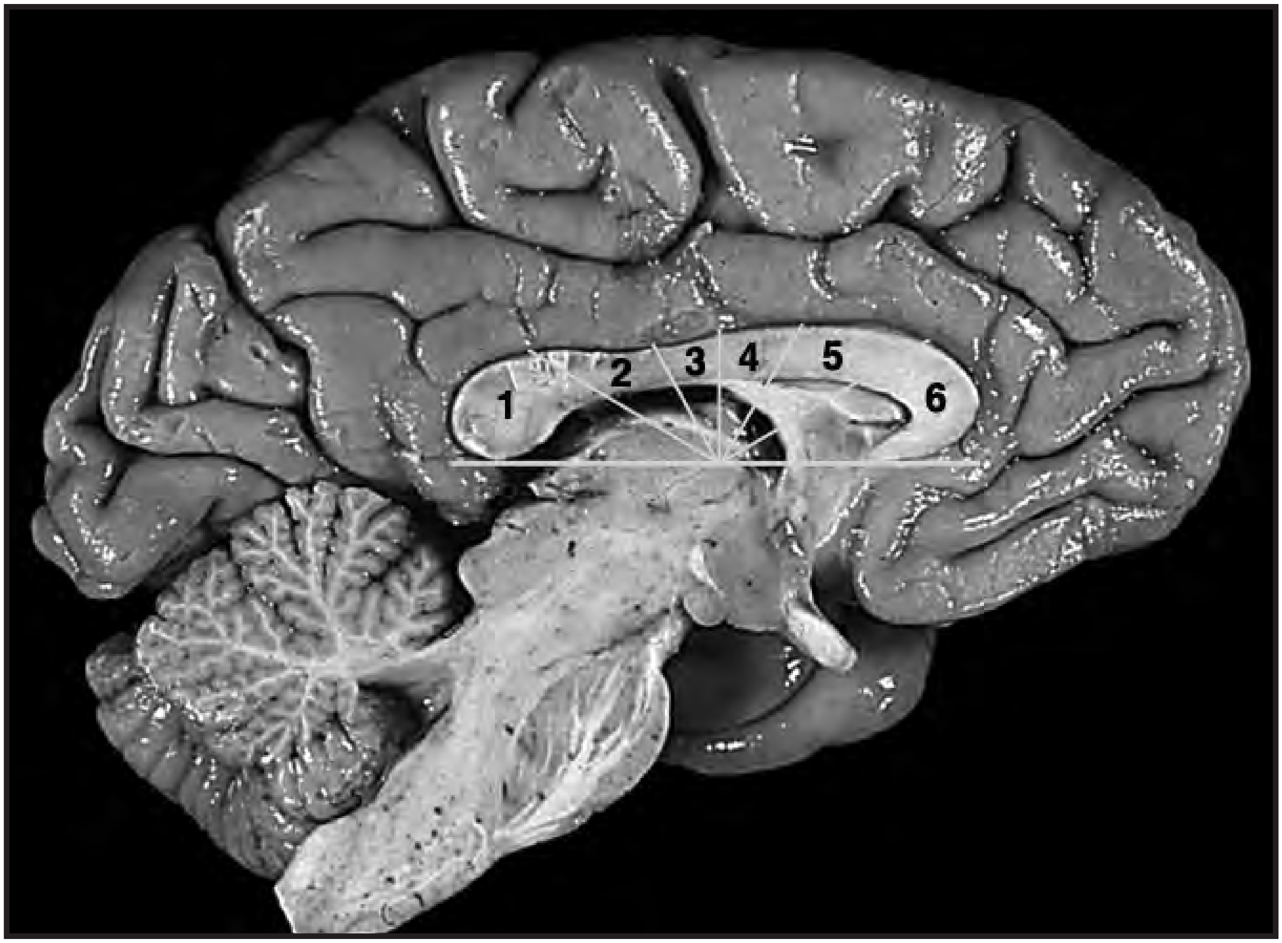

Fig. 3. Midsagittal view of the brain of Pan troglodytes, showing the radial-line method of callosal division. 1: splenium, 2: isthmus, 3: posterior midbody, 4: anterior midbody, 5: rostral body, 6: genu/rostrum.

METHODS

Corpus callosal measurements were performed using postmortem specimens of *M. fascicularis* (male n = 20, female n = 20) derived from the collections of Dr. Patrick Gannon (then housed in the Department of Otolaryngology, The Mount Sinai School of Medicine) and the laboratory of Dr. Ralph Holloway, Department of Anthropology, Columbia University. Brains of *P. troglodytes* (male n = 11, female n = 12) for this study were obtained from Yerkes Regional Primate Center, Emory University (n = 7 brain tissue, n = 6 MRI), the Department of Mammals at the National Museum of Natural History, Smithsonian Institution (n = 6), and the collection of Dr. Ralph Holloway (n = 4).

Morphological analysis

The corpus callosum has been traditionally parcelled into five regions. Although there are no anatomical or histological landmarks defining each region, they can be defined according to a straight rostrocaudal length, dividing the corpus callosum into thirds and fifths to delineate each region (Mall, 1909; de Lacoste and Holloway, 1982; Witelson, 1989; Aboitiz et al., 1992a,b). The different callosal regions defined by this method are (i) rostrum (anterior one-third); (ii) genu (area between the anterior one-fifth and anterior one-third); (iii) midbody (middle one-third); (iv) isthmus (area between the posterior one-third and posterior one-fifth); (v) splenium (posterior one-fifth) (Fig. 2). Further, some researchers (Aboitiz et al., 1992a) divide the midbody into an anterior midbody (area between the anterior one-third and one-half) and posterior midbody (area between the posterior one-half and one-third) (Fig. 3). As a result of these differences in allocating the callosal subregions both methods of the dividing the corpus callosum into either five (straight-line method) or six (radial line) parts were used.

Absolute measurements on the total callosal area and the areas of its regions were recorded using SigmaScan Pro (SPSS Science). In addition, statistical calculations were performed using absolute measurements. The final analyses of the areas calculated on the corpus callosum and the conclusions drawn from these analyses were, however, conducted using only standardized measurements, utilizing Jerison's (1973) slope.

$$\text{(CC measure)}/\text{(Brain Weight)}^{2/3} \quad (1)$$

Histological analysis

Millions of axons of different diameters traverse the corpus callosum. Given the large number of axons occupying any given area in the corpus callosum, sex differences may be manifested in subtle aspects unavailable through purely morphological measurements. While it is prudent to assume that there are no sex differences in the fiber composition of the corpus callosum in the subjects examined here given the considerable lack of sex differences in the morphological dimensions of this structure, it was determined that a histological study of a small number of select individuals would be performed in order to demonstrate this assumption in a timely manner. The region chosen for this portion of the study is the splenium, since it is this callosal region that has arguably undergone the most significant evolutionary change and is most sexually dimorphic in modern humans (de Lacoste and Holloway, 1982; Holloway, 1990).

The splenium in four *M. fascicularis*, two individuals of each sex (male n = 2, female n = 2), and five *P. troglodytes* (male n = 2, female n = 3) were embedded in Epon and sliced into ultrathin sections (< 0.5μm). The sections were then stained with toluidine bluse and examine using a Zeiss Axioskop light microscope. Using bright field emission and a 40x objective lens, histological samples were examined for myelin and cellular integrity. Samples which did not meet specific criteria for myelin integrity were rejected. Each of the *M. fascicularis* individuals chosen for study was deemed appropriate for study, since none of these individuals exhibited any myelin or cellular degradation. Three of the five *P. troglodytes* specimens (YN88-256, YN92-115, YN95-60) were rejected, since all exhibited significant and severe myelin and cellular degradation. Thus, a single *P. troglodytes* female (YN94-67) and single *P. troglodytes* male (YN97-139) were selected. Once the integrity of the specimens was determined, splenial fiber counts were achieved using a 100x oil immersion objective and digital capture. Analysis of the total number of fibers in the splenium was determined using IPLab 3.1 (Scanalytics, Inc.).

RESULTS

Macaca

For *M. fascicularis*, males on average possess an absolutely larger corpus callosum than females. However, when these results are standardized according to brain weight the differences between males and females for total callosal area disappears and are statistically insignificant. Such a result indicates that any cognitive differences between males and females of this species are probably caused by the overall structure of the corpus callosum. In addition, they would also suggest that sex differences in this structure as seen in modern humans (see de Lacoste and Holloway, 1982) likely do not have their origins within the cercopithecoid clade. However, this conclusion may be somewhat presumptuous at this stage when discussing the results of this research, because it assumes that evolution of the corpus callosum results in an overall change in this structure rather than a mosaic alteration.

M. fascicularis does not exhibit any statistically significant difference between males and females either in the absolute or relative size of the genu. The lack of sex differences in this area is unsurprising, since the genu is thought to connect portions of the motor cortex as well as areas within the prefrontal cortex (Pandya et al., 1971; de Lacoste, 1981; Seltzer and Pandya, 1983; Barbas and Pandya, 1984). Differences in this region should not be suspected, simply because there is little information to suggest that male and female members of *M. fascicularis* differ from each other with regard to motor skills. In addition, while fibers traversing this region of the corpus callosum connect portions of the orbitofrontal cortex, which is important for both memory and behavior (Parker et al., 1997), there is little information in *Macaca* suggesting that males and females differ significantly in these tasks (Lacreuse et al., 1999).

The anterior and posterior midbodies represent the two divisions of the midbody defined using the straight and radial line methods. The anterior portion of this region contains interhemispheric fibers connecting the primary, secondary, and supplementary motor cortices, while the posterior portion connects primary and secondary sensory areas (Pandya et al., 1969; de Lacoste, 1981; Pandya and Seltzer, 1986). In addition, the posterior portion of the midbody possesses fibers connecting the postcentral and posterior parietal lobe as well as portions of the superior and inferior temporal lobes (de Lacoste, 1981; Seltzer and Pandya, 1983; LaMantia and Rakic, 1990a). Despite the complexity of the connections passing through this region, the midbody areas for males and females of *M. fascicularis* do not differ significantly from each other. Albeit these results are not unusual when compared to the human data (Oppenheim et al., 1987; Allen et al., 1991; Witelson, 1989; Matano and Nakano, 1998), they are somewhat unexpected given the role of callosal axons passing through the midbody in sexually dimorphic tasks.

The splenium represents the region of the corpus callosum that has often been found to exhibit sexual dimorphism in humans (Holloway, 1990; Holloway et al., 1993; Davatzikos and Resnick, 1998). Moreover, area differences between males and females do not appear to be the result of isometric expansion of the splenium in one sex versus the other. Instead the relatively larger splenium of human females is also more bulbous than that of males (de Lacoste and Holloway, 1982; Holloway et al., 1993; Davatzikos and Resnick, 1998). Since the splenium is responsible for connecting occipital, temporal, and posterior parietal areas of the brain (Pandya and Seltzer, 1986; Gazzaniga, 2000), it is possible that these area and form differences may be related to sex differences in visuospatial, language, and somatosensory cognitive functions.

The splenium of the *M. fascicularis* sample used in this study did not exhibit any sex differences. While males possessed absolutely larger splenia using the straight and radial-line methods, this difference was eliminated when brain size was taken into account. In fact, the samples overlap entirely. Since the composition and form of the corpus callosum appears to be the result of cortical size and function, it is unlikely that the hypothesis that there are sex differences in the corpus callosum of cercopithecines would be true.

Pan

Female *P. troglodytes* possess an absolutely and relatively larger corpus callosum. However, these differences are statistically insignificant. Despite the lack of a significant difference between males and females, it is worth noting that unlike *M. fascicularis* the corpus callosum in *P. troglodytes* trends toward being larger in females. Measurements of total callosal area provide some information regarding the presence of sexual differences of the structure, but they do not provide specific information that may be useful for the assessment of possible lobular or cognitive differences in the brain. To gain insight into such differences when examining the midline profile of the corpus callosum it is necessary to examine callosal regions. Below the results for each region are discussed.

The genu as defined using the straight-line method is roughly equivalent to the genu and rostral body as defined through the radial-line method. As such these areas occupying the anterior one-fifth of the corpus callosum will be referred to as the genu here. For both the straight and radial-line methods females possess an absolutely larger genu than males. However, the relative values of this structure do not indicate any difference between males and females. In addition, there is no statistical difference between males and females in the genu. The lack of a significant difference between males and females in the genu means that sex differences in this region as displayed in humans (Witelson, 1989) must have evolved after the ape-human split.

Both the absolute and relative values for midbody area differences between males and females are statistically insignificant for *P. troglodytes*. The averages for the anterior and posterior midbody using the straight-line and radial-line methods display significant overlap, such that there is no apparent trend towards one sex possessing a slightly larger midbody than the other. For example, the greatest difference between males and females occurs when the averages of the relative size of the anterior midbody as defined using the straight-line method are compared. The average relative size of the anterior midbody is 0.0095cm^2 for females and 0.0086cm^2 for males. However, the standard deviation of the sample is large, and thus there is a significant degree of overlap. The lack of sexual differences in this area, though, is expected, since the areas of the brain connected by fibers passing through this region have not become highly specialized over the course of primate evolution. Moreover, humans do not display any sexual differences in this area (Witelson, 1989), and as such it is not expected that *Pan* would.

The isthmus of the human corpus callosum displays sexual dimorphism with females possessing a relatively larger isthmus than males (Witelson, 1989; Steinmetz et al., 1992; see also Davatzikos and Resnick, 1998). Due to this relationship it is hypothesized that female *P. troglodytes* may also possess a relatively larger isthmus. Indeed females possess an absolutely and relatively larger isthmus on average as defined using the straight-line method. However, there is a large degree of overlap between the two samples, and thus there is not a statistically significant relationship between sex and isthmus size. This means that any statistically significant sex differences in this region are unique to humans, and must have evolved after the ape-human split. Alternately, chimps may have retained the earliest trends toward such a dimorphism.

The splenium of the corpus callosum has been an area of intense interest in human studies (de Lacoste and Holloway, 1982; Oppenheim et al., 1986; Holloway, 1990, 1993). Bean (1906) had first described the splenium of females as being different from males. Later studies found similar differences and described the female splenium as more bulbous. This general description has become useful in identifying the corpus callosum of human females, although the functional significance of this morphology has not been deciphered. Some researchers, though, have suggested that despite this general morphological dissimilarity between males and females sex differences in the human splenium do not exist (e.g., Witelson, 1989). Due to the disparity of splenial data from humans it is not possible to predict the presence of sex differences in this region in *P. troglodytes*. Indeed, there is not a significant difference between male and female *P. troglodytes* for area measurements of the splenium using the straight or radial line method.

Histology

Regional and total area measurements of the corpus callosum provide useful information of the overall structure of this interhemispheric highway. In their study of the composition of the corpus callosum, LaMantia and Rakic (1990a) found no appreciable difference between a single male and female *M. mulatta* for the total number of fibers comprising this structure. Concurring with LaMantia and Rakic (1990a), this current study found no difference in the number of fibers comprising the splenium as well as the total number of fibers inferred to compose the entire corpus callosum in both *M. fascicularis* and *P. troglodytes*. This is consistent with results on morphological measurements of total and regional callosal area (LaMantia and Rakic, 1990a; Aboitiz et al., 1992a; see also Highley, 1999). However, contra to LaMantia and Rakic, (1990a) who suggest that males have slightly more axons in the corpus callosum than females, this study found that females possess slightly more axons than males. From this it can be assumed that there is a large degree of variability expressed in *Macaca* with regard to the total number of axons in the corpus callosum. In addition, this study concurs with the conclusion of Aboitiz et al. (1992a), which states that if the overall area of a callosal region does not demonstrate sexual dimorphism then one would not expect to find a difference in the number of fibers comprising that area.

In humans, Aboitiz et al. (1992a) found no appreciable difference between males and females in the number of fibers comprising the corpus callosum. This would indicate that even apparent sexual differences in the size of the corpus callosum do not impart any correlation to its composition. Aboitiz et al. (1992a) predict that the area of the corpus callosum is a good indicator of the number of fibers contained in it. However, they go on to acknowledge that this predictive hypothesis may not be accurate for estimating the number of gigantic fibers (> 3μm in diameter). For this reason it is not possible to propose the presence or lack of sex difference in the corpus callosum by merely estimating the total numbers of fibers it contains. Instead it is necessary to additionally account for the types of fibers comprising the corpus callosum. Thus, counting the total number of fibers in the corpus callosum is only one step to the conclusion of assessing sexual dimorphism in this structure.

There is no significant difference between *M. fascicularis* males and females with regard to fiber type (Fig. 4; Table 1). While these results combined with those from other aspects of this study conclusively show that there are no sex differences in the corpus callosum of this species, they can be discussed descriptively to provide information that may be useful for drawing a hypothesis on the evolution of sex differences in the brain. Males of this species tend to possess more medium, large, and very large axons than females. Females conversely tend to possess more small axons than males. While the differences between males and females are not statistically significant, this descriptive information does offer some insight into relative differences between males and females.

The differences between the male and female *P. troglodytes* sampled do not appear to be significant (Table 2). Proportionally, the female possesses a greater number of fibers than the male, but based on data from macaques (LaMantia and Rakic, 1990a) and humans (Aboitiz et al., 1992a; Highley et al., 1999) this type of variation between individuals for total callosal axon number is not unusual. While the difference in the total number of axons in the corpus callosum between the male and female sampled demonstrate that sex differences in this structure most likely do not exist, it is, nevertheless, possible to discuss the general differences in the types of fibers found in the splenium of these individuals.

The male *P. troglodytes* sampled possesses more small and large diameter axons than the female, while the female possesses more medium, very large, and giant axons than the male. While this cannot be tested statistically due to the small sample size, it can be assumed by examining the number of axons in each category and their percentage to the total number of axons that there is not sexual dimorphism with regard to types of fibers in the splenium of the corpus callosum. This data can provide basic descriptive information regarding possible sex differences in this species and the evo-

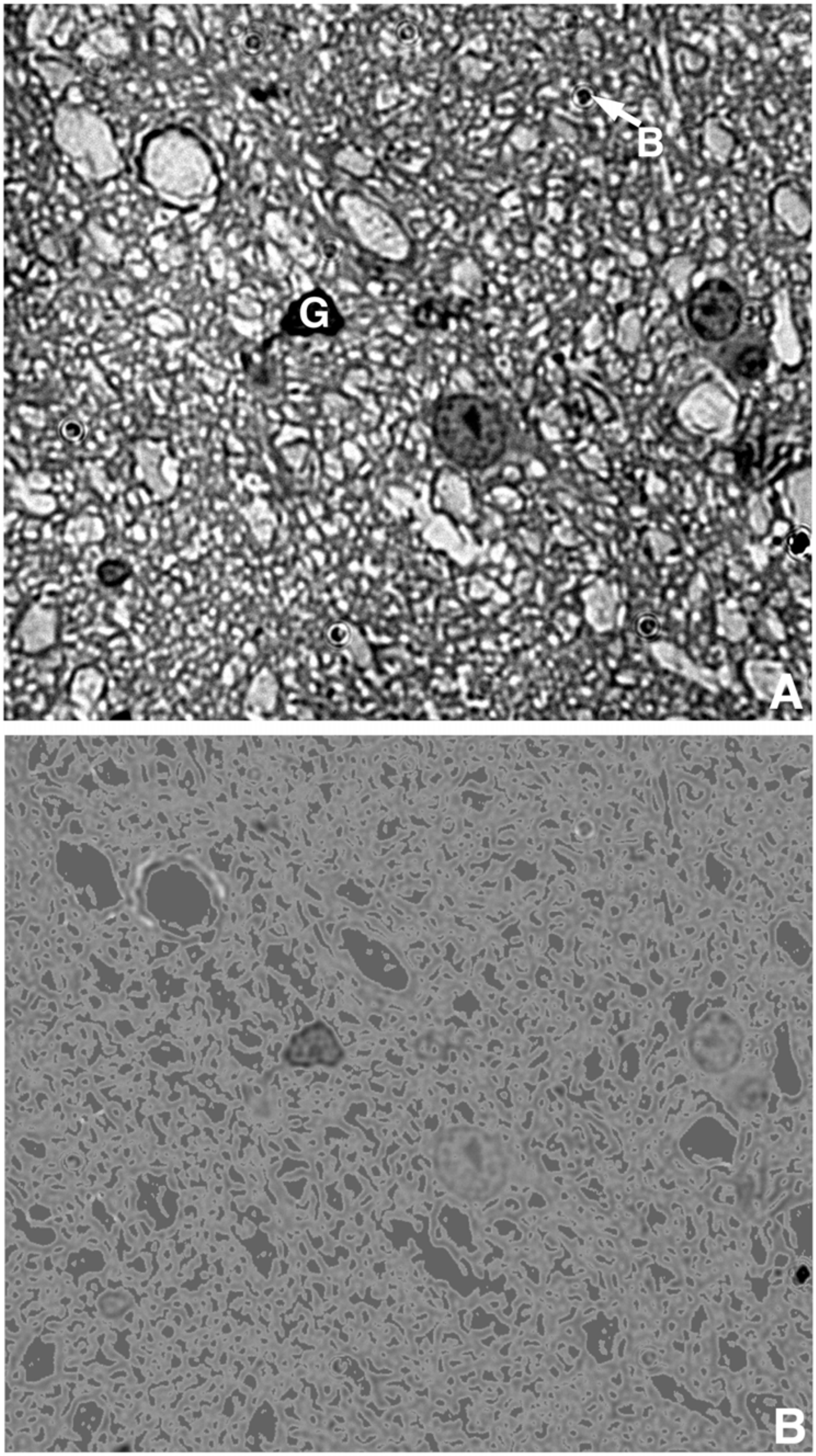

Fig. 4. Histological section (1000x) from the splenium of Macaca fascicularis, showing the counting regime of the IPLab software. unsampled section. Figure B is the same section indicating the cells counted by IPLab. G: glial cell, B: air bubble. The latter features are manually removed before the end count is made.

Table 1. Splenial axon number based on axonal size for Macaca fascicularis[1]

Specimen	Sex	Very large axons (≥ 2.5µm)	Large axons (1 - 2.5µm)	Medium axons (0.4 – 0.99µm)	Small axons (< 0.4µm)
PGM 40	F	7073 (.09)	20768 (.28)	27250 (.36)	19956 (.26)
PGM 54	F	4875 (.13)	10831 (.30)	13001 (.36)	7447 (.21)
PGM 43	M	6017 (.12)	14050 (.28)	16136 (.32)	13915 (.28)
PGM 45	M	6220 (.13)	14999 (.31)	16606 (.35)	9906 (.21)

1. Total number of axons for each axon category. Percentage to the total number of axons in the sampled area is listed in parentheses. Percentages are rounded up. M = male, F = female.

Table 2. Splenial axon number based on axonal size for Pan troglodytes1

Specimen	Sex	Giant axons (≥5µm)	Very large axons (2.5 - 5µm)	Large axons (1 - 2.5µm)	Medium axons (0.4 – 0.99µm)	Small axons (< 0.4µm)
YN94-67	F	62 (.06)	197 (.18)	277 (.25)	370 (.34)	181 (.24)
YN97-139	M	50 (.03)	276 (.18)	438 (.28)	495 (.32)	284 (.22)

1. Total number of axons for each axon category. Percentage to the total number of axons in the sampled area is listed in parentheses. Percentages are rounded up.

lution of sex differences in general. For example, the female *P. troglodytes* possessed more medium and very large fibers than the male, while the female *M. fascicularis* were found to possess only more small axons than the males. This difference as expressed in *Pan* is similar to the result obtained by Aboitiz et al. (1992a) for humans, speculatively implying that the structure of the corpus callosum in *Pan* is more similar to humans than to cercopithecoids.

DISCUSSION

The conclusion of this study is that based on measurements of the total midsagittal area of the corpus callosum, midsagittal regional areas of the corpus callosum, and the number and type of axons in the splenium of the corpus callosum, there are no sex differences in this structure in *M. fascicularis* or *P. troglodytes*. Indeed, neither species exhibits a statistical trend, indicating that one sex may possess a larger callosum, more axons, or more of a particular type of axon. From these results it is also possible to conclude that modern humans are the only extant primate group that exhibits any sexual dimorphism in the corpus callosum or its regions. In some ways these results are consistent with the literature suggesting specialized lateralization of the human brain and sex differences exhibited in lateralized cortical processes (e.g., Witelson, 1977; Kimura, 1980, 1983; Hugdahl et al., 1993; Eviatar et al., 1997; Crucian and Berenbaum, 1998; Halpern et al., 1998; Hausmann and Gunturkun, 1999; Vallortigara et al., 1999; Amunts et al., 2000; also see review by McGlone 1980). This is because many lateralized processes often are related to functions of speech and language, which have never been isolated in nonhuman primates.

Despite the apparent lack of lateralization in the nonhuman primate brain with regard to language, there have been other studies that indicate the brain of nonhuman primates may be lateralized (e.g., Gannon et al., 1998). However, many of these studies depend on correlations between handedness and a given task (Note: the author disagrees with the usage of the term handedness as it has been applied in many of the following psychological studies and prefers the term hand preference). For example, Bard et al. (1990) found that *P. troglodytes* displays a general right hand preference during feeding behaviors. At the same time Hopkins (1990) found that *P. troglodytes* and *Pongo* display a general right hand preference in an experimental model requiring subjects to manipulate a joystick (see also review by Hopkins and Morris, 1993). Later, Hopkins and his colleagues have correlated hand preference to birth order (Hopkins and Dahl, 2000), gestural communication (Hopkins and Leavens, 1998), and other manipulation tasks (Hopkins and Pearson, 2000). Although these particular studies do not provide definitive data on the lateralization of the nonhuman primate brain, they do provide a means to understand the origins of laterality.

Recent anatomical asymmetries have been noted in the brains of great apes but not Old World or New World monkeys (Hopkins and Rilling, 2000; Hopkins and Marino, 2000). In their study on petalial patterns in primates using left and right anterior frontal, posterior frontal, parietal, and occipital cerebral width measurements on axial magnetic resonance images, Hopkins and Marino (2000) found that the great apes (*Pan*, *Gorilla*, *Pongo*) display a right-frontal, left-occipital directional asymmetry or petalia pattern. While there was an individual from each taxon that displayed the converse asymmetry, the results for these genera were more consistent than for other groups. That is, Old and New World genera did not display directional asymmetry, albeit certain individuals within the *M. mulatta* sample did. Working from the same dataset Hopkins and Rilling (2000) report that measured asymmetries in neocortical surface area and brain volume indicate that the brains of the great apes are more asymmetrical than those of Old and New World monkeys. Moreover, this particular study suggests that individuals that possess a more leftward asymmetric brain had a smaller corpus callosum than those individuals that displayed rightward or no asymmetry. Handedness (hand preference) data collected by Hopkins (1995) and Westergaard et al. (1998) suggest that there is a general shift in primates from population-level left-hand preference to population right-handedness for quadrupedal and bipedal reaching such that *Pan* more often displays a preference for right handed reaching and manipulation than Old and New World primate groups. Moreover, individuals that display right-handedness or right hand preference possess a smaller corpus callosum as a function of neocortical surface area and brain volume (Hopkins and Rilling, 2000). While this finding cannot confirm the presence of lateralized brain function in any of these species studied, especially *Pan*, it does suggest an early evolution for the development of lateralization.

Experiments designed to test cognitive skills in nonhuman primates, such as handedness, provide important data that can be used to formulate hypotheses concerning the origins of brain lateralization as well as the development of sex differences in the brain. In addition to handedness or hand preference studies, other behavioral experiments have been report that may enhance these evolutionary and cognitive hypotheses. Data collected from memory and cognitive performance studies on nonhuman primates indicate that certain male-female differences occur. In particular, several studies have found that male and female *M. mulatta* differ from each other with regard to facial discrimination tasks (Buccafusco et al., 1999; Lacreuse et al., 1999; Parr et al., 2000). For example, Buccafusco et al. (1999) reports that male *M. mulatta* performed better on memory-related tasks compared to females, although these tasks required simple memory recall, and not recall of complex subjects.

Complex subject recall requires the individual to not only recall specific subject matter, but also associated features of the item in question. In humans such complex tasks are usually associated with language tasks (Hugdahl et al., 1993; Hadar et al., 1998; Hausmann and Gunturkun, 1999). For example, when an individual is required to recognize familiar faces prefrontal and lateral temporal regions are bilaterally activated. However, when an individual is exposed to newly learned or unfamiliar faces hippocampal, parahippocampal, parietal and anterior temporal activation is observed (Clark et al., 1998; Leveroni et al., 2000). Observations such as these are significant, since these tasks, except for the hippocampal responses, require the participation of callosal axons. Moreover, males and females are dissimilar from each other for these and many cognitive tasks involving language areas (Shaywitz et al., 1995; Levin et al., 1996; Gur et al., 1999; see also Kimura, 1983, 1987).

Although macaques do not possess cognitive abilities approaching those of humans, studies on these nonhuman primates indicate that they possess some ability to perform tasks such as facial recognition and recognition of facial cues (Vermeire et al., 1998; Parr et al., 2000). While it is not currently possible to test nonhuman primates with PET or fMRI to determine the specific functional areas of their brain, it is possible to use topographic studies to draw some correlations between cortical anatomy and possible cognitive functions. Work by de Lacoste (1981), Pandya and his colleagues (Pandya et al., 1969; Seltzer and Pandya, 1983; Barbas and Pandya, 1984), and LaMantia and Rakic (1990a,b) indicate that humans and macaques share many functional areas within the cerebral cortex. From such correlations it is possible to hypothesize that if sex differences exist with regard to certain cognitive functions that males and females may demonstrate differences in the callosal fibers associated with those tasks. For facial recognition tasks these fibers likely, in part, pass through the midbody of the corpus callosum. Thus, it is probable that the midbody would be different between males and females. The data presented here, though, concur with measurements on humans indicating there is no difference between males and females in the area of the midbody of the corpus callosum (Oppenheim et al., 1987; Allen et al., 1991; Witelson, 1989; Matano and Nakano, 1998).

The above behavioral studies are restricted to *Macaca*, but other data also provide important information suggesting the presence of sex differences in the brains, and possibly the corpus callosum, of nonhuman primates. Two recent studies involving *P. troglodytes* suggest that this species possesses memory and recall abilities that exceed those displayed by *Macaca mulatta*. In the first study, Menzel (1999) reports the ability of a single female *P. troglodytes* that retained the ability to recall the locations of randomly hidden objects for up to sixteen hours. In the second study, Parr et al. (2000) report that *P. troglodytes* displays a greater recall of conspecifics facial features than *Macaca mulatta*. In this last report chimpanzee individuals were required to match similar pictures of conspecifics. While both the *Macaca mulatta* individuals and chimpanzees displayed an equal ability to discriminate conspecifics, the *Macaca mulatta* individuals required significantly more trials to be able to perform the task successfully. Although these reports could be described as rudimentary behavioral studies, they do still suggest the possible presence of specialization (and possibly lateralization) in the nonhuman primate brain.

Three final studies that are more relevant to the current study than many of those discussed above include spatial experiments performed on *Macaca mulatta*. This is because both of the following studies not only discuss the likely presence of lateralized function in parts of the nonhuman primate brain, but also the presence of sex differences on spatial tasks. In an experiment on twenty-six split-brain *Macaca mulatta*, Vermeire et al. (1998) found that faces were better remembered by the right hemisphere than the left. In addition, they also found that females monkeys were more lateralized for learning to discriminate faces than were males. A later study by Kavcic et al. (2000) agrees with the above findings that left hemisphere dominance for certain visual-memory tasks occurs in *Macaca*. Finally, work by Lacreuse et al. (1999) shows that *Macaca mulatta* displays sex differences with regard to spatial ability. However, it should be noted that Lacreuse et al. (2000) found a decline in spatial ability among males as they age, such that old males perform no better than old females. Yet for any given age class, except this late one, males outperform females in spatial cognitive tasks.

The studies discussed above report provocative results that suggest the presence of lateralization for certain tasks in nonhuman primates. While chimpanzees seem to possess greater asymmetry and cognitive abilities than macaques, macaques do appear to exhibit some lateralization in cognitive function. Moreover, males and females differ in some of these functional tasks. This later point, though, is contradicted by the results of this study and those of reports such as Hopkins and Rilling (2000). Hopkins and Rilling (2000) suggest that the brains of macaques are not as lateralized as those of chimpanzees. This would imply that spatial, memory, or other cognitive tasks are not lateralized in Old World monkeys. In addition, the information provided here suggests that males and females should not perform differently for these tasks. However, these hypotheses assume that the corpus callosum must be integral to all cognitive tasks. This, though, is not the case.

First, the various reports that suggest lateralization of the nonhuman primate brain rely upon what has been described as handedness (more properly hand preference) and visual capabilities. While tasks related to these features may be useful in understanding cognitive tasks and callosal function, there is no known study that adequately demonstrates the existence of higher cognitive processes in nonhuman primates. Because of this disparity between human and nonhuman primate studies, many of the results that suggest laterality in function may be explained as proving not the existence of complex pathways traversing the corpus callosum or specific lateralization of the neocortex, but as lateralization in basic mammalian cognitive tasks involving more primitive pathways such as the superior colliculus, anterior commissure, and hippocampal commissure, all of which are capable of carrying the type of information investigated in the afore mentioned reports.

Secondly, the studies that report sex differences in cognitive performance utilize visual information. While the splenium of the corpus callosum is important for relaying visual information, the type of visual discrimination described by Kavcic et al. (2000) and Vermeire et al. (1998) can occur via the superior colliculus (Wright and Craggs, 1976; Sommer and Wurtz, 1998). In addition, results showing sex differences in throwing among capuchin monkeys (Watson, 2001) may occur via sex differences in the anterior commissure (see Noonan et al., 1998). Although this does not eliminate the likelihood of lateralization of visual and motor components of the cerebral cortex in nonhuman primates, the possibility that these sex differences occur as the result of other hemispheric pathways explains why it is possible to suggest lateralization of and sex differences in the brain of nonhuman primates, yet to not find sex differences in the corpus callosum.

In general, there is a wealth of information that implies the presence of lateralized function within the brains of macaques and chimpanzees (see above discussion). These studies, though, lack the sophistication to ally simple visual and motor functions of the nonhuman primate brain with higher cognitive processes involving the integration of data as seen in humans. It is probable that some lateralization exists within the nonhuman primate brain, albeit not at the level present in modern humans. Indeed, the results of Hopkins and Rilling (2000) study would say that the degree of lateralization is different between macaques, chimpanzees and humans with humans displaying the most asymmetric brains in this group and macaques the least. However, the question still remains, is the level of asymmetry seen in great ape brains sufficient to produce human-like cognitive functions?

Based on behavioral data the answer remains unresolved. A lack of cerebral laterality in nonhuman primates, though, does not preclude one from suggesting that the corpus callosum would not be expected to display sexual dimorphism in either midsagittal area or axonal composition until the brain is sufficiently lateralized in function. This can be assumed because none of the above studies examines cognitive functioning at a level sufficient to assume the corpus callosum has been co-opted for the task of interhemispheric integration of cognitive information. Such information could only be approached through invasive retrograde histology or PET and fMRI studies. To conclude, the above studies are useful in understanding the evolution of the brain and sex differences within it, but they do not contradict the results of this study, which concludes that sex differences do not exist in the midsagittal area or axonal composition of the corpus callosum of nonhuman primates.

The uniqueness of the human brain has been discussed for thousands of years since the times of the Egyptians, Aristotle, and Descartes with little resolution (see Finger, 1994). Moreover, its has been a contentious topic in anthropology since the days of eminent neuroscientists/anatomists/anthropologists such as Broca, Smith, Dart, and Anthony (see Holloway, 1997). There is, however, still disagreement concerning the advent of human-like features in the brain, which eventually led to human cognitive abilities. Recently, Ambrose (2001) has revived an idea first proposed by Holloway (1970) and later revisited by Calvin (1983, 1993) and Wilson (1998) hypothesizing that the need for accurate throwing and tool making skills created selective pressures for advancement of the hominin brain, and in turn the development of sex differences in the cerebral cortex. These selective pressures also aided the development of sex differences in the modern human brain. While there are other hypotheses for the evolution of the human brain (e.g., Tobias, 1971; Jerison, 1973; Gould, 1977; Gould and Lewontin; 1979; Falk, 1990), few have been visited as frequently as Holloway's "throwing theory". This, though, has not quelled the debate of general human brain evolution or the development of sex differences in the brain, since the data that may be used for such studies is merely corroborative. The paucity of endocasts in the fossil record and the limitations of endocasts restrict their ability to provide conclusive answers of primate brain evolution. In addition, behavioral data on human and nonhuman primate subjects can provide information on cortical and cognitive functions of extant brains. However, an examination of both types of data, fossil and living, can be used to develop robust theories of brain evolution. In the case of this study it is possible to propose a hypothesis about the advent of sex differences in the corpus callosum of the primate brain.

The results of this study indicate that sex differences in the corpus callosum did not develop until after the ape-human split some 7 – 5 million years ago. Indeed, sex differences in this interhemispheric pathway may not have developed until the advent of our own species some 200,000 years ago. Neither *M. fascicularis* nor *P. troglodytes* display sex differences in total callosal area or the area of individual callosal regions. Moreover, neither species shows a difference between males and females for the number or types of fibers comprising the splenium of the corpus callosum. One would be inclined to conclude that these statements are possible, since the results do not exhibit statistical significance or a statistical trend.

From the results obtained here it seems apparent that sex differences in certain cognitive features represent an evolutionarily recent phenomenon. However, the finality of these results should be questioned, since it is difficult to assume that sex differences in the corpus callosum and cognition must be statistically significant. While the results reported here are not significant, lending confidence to the conclusions discussed above, the general patterning of sex differences in *M. fascicularis* versus *P. troglodytes* may provide important clues as to when sex differences resulting in differences in cognitive performance came about. The results for *M. fascicularis* show that there is complete overlap in the relative size of the corpus callosum and its regions between males and females. From this it is possible to conclude that the corpus callosum is not wholly responsible for the differences between males and females in the performance of certain tasks. The results for *P. troglodytes*, though, do show a tendency for females to possess a slightly larger corpus callosum, genu and isthmus than males, albeit these distinctions are not statistically significant. In addition, distribution of the types of axons passing through the splenium in *P. troglodytes* is similar to the distribution seen in modern humans in that the female possesses more medium, very large, and giant axons than males (Aboitiz et al., 1992a). While this does not suggest that the corpus callosum of humans and chimpanzees are similar in their composition and fiber distribution, it does pose an interesting question. What level of uniqueness in the human corpus callosum is required to separate its features of form, function, and sexual dimorphism from that of chimpanzees?

The corpora callosa of great apes and humans are smaller relative to neocortical surface area and brain volume. From this it is assumed that the brains of great apes and humans are more lateralized than either Old or New World monkeys (Rilling and Insel, 1999; Hopkins and Rilling, 2000; see also Gannon et al., 1998). In addition, the findings of Hopkins and Marino (2000) suggest that the great apes possess a torque pattern similar to modern humans. Despite these general comparisons, though, these results do not imply that the brains of great apes and humans are alike. More importantly they indicate that the evolution of the human brain has been largely the result of a long, continuous evolution throughout primate history, and not rapid punctuated change, albeit this is conjecture. These studies as well as those testing for lateralization of the brain for certain cognitive and motor functions do suggest that *Pan* possesses a more lateralized brain than its cercopithecoid relatives. However, data on *Pan* behavioral, motor, and visual tasks do not suggest that *Pan* possesses a degree of lateralization in the cerebral cortex that would permit cognitive functioning beyond the level of a modern human two year old child (Deacon, 1997; Savage-Rumbaugh et al., 1998). The fact that *Pan* may possess a degree of lateralization approaching but not mimicking the human condition helps to explain why *Pan* would display a callosal morphology and composition similar to humans yet not possess similar cognitive characteristics. This observation that the brain and corpus callosum of *Pan* are similar but not the same as those of modern humans also explains why one does not find sex differences in the corpus callosum. That is, the brain of *Pan* has not become sufficiently specialized at the species level to permit the development of measurable sex differences in neocortical components and the corpus callosum.

There are several cognitive differences between males and females. These include differences with regard to visuospatial, motor, and language skills. While it is likely that visuospatial and motor skills contributed to the expansion and reorganization of the hominin brain (Holloway, 1970), one can argue that the most significant consequence of human evolution in general and human brain evolution specifically has been the development of complex language abilities.

The similarities between the brain and corpus callosum of *Pan* and humans can be used to express the uniqueness of each species. As discussed above, *Pan* appears to approach the neocortical condition of humans but does not mimic it. This explains why sex differences in the brain and corpus callosum of *Pan* do not approach statistical significance. It also explains why certain brain structures such as the planum temporale and petalial pattern may display asymmetry in *Pan* but do not confer human-like cognitive functioning (Gannon et al., 1998; Hopkins and Leavans, 1998; Rilling and Insel, 1999; Hopkins and Marino, 2000; Hopkins and Rilling, 2000). This difference between human nonhuman primates is best understood by examining the issue of language.

Several studies have attempted to assign some level of language to *Pan* (Savage-Rumbaugh et al., 1998). However, regardless of the displayed "intelligence" of study subjects, none have ever been able to express communicative abilities beyond those capable in a normal two and a half year old child. This is not to imply that *Pan* does not express some level of intelligence but instead indicates the mere differences between the brain of *Pan* and the brains of modern humans. For example, Gannon et al. (1998) found that human-like asymmetry can be found in the planum temporale of *P. troglodytes*. While this level of asymmetry in humans is thought to result in or represent a product of the laterality of language, the authors do not express any intent to align the language skills of *Pan* and humans. This is because it is difficult to assign advanced cognitive functions such as language to asymmetry in one single structure. In this case asymmetry in the planum temporale may confer laterality in certain cognitive processes in both *Pan* and humans, but it does not presume language in both species.

The role and relationship of the corpus callosum in speech and language has been well established (O'Kusky et al., 1988; Zaidel et al., 1995; Rumsey et al., 1996; Moffat et al., 1998; Gazzaniga, 2000; Habib, 2000; Preis et al., 2000; Shevtsova and Reggia, 2000). The size of the corpus callosum has been shown to be related to the lateralization of language function (Witelson, 1995; Zaidel et al., 1995). In addition, women, who are thought to be less lateralized than men for language, possess a larger corpus callosum and more bulbous splenium (de Lacoste, 1981; de Lacoste and Holloway, 1982; Kimura and Harshman, 1984; Witelson, 1991, 1995; Holloway et al., 1993; Moffat et al., 1998). The presence of continued argument as to the existence of sex differences in the corpus callosum of humans attest to the degree of difference between males and females, which in some cases is small. However, it is still uncertain how much of a difference must occur between the brains of two individuals or the sexes to obtain significant differences in cognitive features. For example, it is generally accepted that males and females differ from each other in certain cognitive skills (Kimura, 1987; Hugdahl et al., 1993; Halpern et al., 1998; de Courten-Myers, 1999; Hausmann and Gunturkun, 1999; Amunts et al., 2000). Yet, each sexually dimorphic skill does not correlate to an equally sexually dimorphic neuroanatomical area, albeit certain areas such as the motor cortex do exhibit direct correlations (de Courten-Myers, 1999; Amunts et al., 2000). Nevertheless, these gaps in human research leave the question of how sexually dimorphic the splenium must be to permit one sex to possess greater integrative capabilities with regard to language and visuospatial skills remains unresolved. Without the resolution of these particular issues the specific role of sex differences in the corpus callosum will remain uncertain.

The when, where, why and how of the evolution of language are questions that are not easily answered. This is because data relevant to these questions must be derived from at least three mutually exclusive categories: living nonhuman primates, living humans, and endocasts of fossils. As mentioned above communicative information in nonhuman primates like that being produced by Sue Savage-Rumbaugh and others attest to the level of skill in species such as *P. troglodytes* and *P. paniscus*. However, these studies do not specifically prove the existence of language or language areas in nonhuman primates or *Pan* in particular. They do, though, shed some light on the development of language. Based on these behavioral studies and the anatomical studies mentioned above, it is possible that *Pan* possesses certain brain structures and a degree of cerebral lateralization that permit *Pan* to communicate at a level beyond other nonhuman primates. Though this level of cerebral and cognitive development is not the same as displayed by humans, it does provide provocative evidence for the existence of a cerebral archetype early in human evolution rather than the arise of areas such as Broca's and Wernicke's *de novo* in *Homo sapiens*.

The fossil record appears to support this claim. Although endocasts of australopiths do not appear to be significantly different from *Pan*, later species such as *Homo habilis* and *Homo erectus* do begin to display human-like proportions and features (Tobias, 1975; Holloway, 1981a,b; Broadfield et al., 2001). The presence, though, of human-like features does not necessarily confer the capacity for modern human speech and language on any species other than modern humans. However, they do indicate that the development of neuroanatomical features related to speech, language, and visuospatial skills may have existed long before the arrival of *Homo sapiens*. As to the role of these features for the development of sex differences in the corpus callosum, in particular the splenium, the development of certain higher cognitive features of the brain should precede the development of sex differences in those functions (speech, language, and visuospatial skills) as well as sex differences in the neuroanatomical structures related to those functions. Sex differences in the corpus callosum would thus not be expected in taxa such as *Pan* and *Macaca*, since neither species possesses the neuroanatomical substrate for modern human speech, language, and visuospatial skills or the degree of lateralization of the cerebral cortex required to produce the specialized features of language. Due to the role of the splenium in connecting modern human language areas, it is suspected that if a particular species is to possess communicative features comparable to humans then this area may display sex differences as it does in humans. However, since *Pan*, as mentioned above, does not possess human communicative abilities, visuospatial skills, or the neuroanatomical substrate that would lead one to propose the ability for human-like communication or visuospatial skills, one would not expect to find sex differences in this particular callosal region. Humans, therefore, are unique among living primate taxa in possessing a highly lateralized, sexually dimorphic brain and corpus callosum.

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