

Gender-based differences in the shape of the human corpus callosum are associated with allometric variations

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Abstract

The corpus callosum displays considerable morphological variability between individuals. Although some characteristics are thought to differ between male and female brains, there is no agreement regarding the source of this variation. Biomedical imaging and geometric morphometrics have provided tools to investigate shape and size variation in terms of integration and correlation. Here we analyze variations at the midsagittal outline of the corpus callosum in a sample of 102 young adults in order to describe and quantify the pattern of covariation associated with its morphology. Our results suggest that the shape of the corpus callosum is characterized by low levels of morphological integration, which explains the large variability. In larger brains, a minor allometric component involves a relative reduction of the splenium. Small differences between males and females are associated with this allometric pattern, induced primarily by size variation rather than gender-specific characteristics.

Key words: brain shape; sexual dimorphism; shape analysis.

Introduction

Morphological variation of the human corpus callosum has been extensively investigated in terms of shape and size. The functional relevance of this brain component in normal inter-hemispheric communication and in its pathological manifestations is widely acknowledged. The midsagittal contour of the corpus callosum delineates a fuzzy but clearly recognizable element, both through anatomical dissection and biomedical imaging. Dissection studies were limited by post mortem effects on tissues, as well as by specimens and sample availability, hampering large statistical approaches. Imaging has definitively resolved these two analytical restrictions. Because of the paucity of geometrical references along the corpus callosum outline, many morphological analyses were limited to the comparison of surface and volume. The advances associated with landmark-based morphometrics have partially resolved this constraint, allowing a quantification of shape components (Bookstein, 1997). Most of the quantitative studies concern

corpus callosum shape variation in pathological conditions (Bookstein et al. 2001, 2002). However, despite the efforts invested in studying the morphology of the corpus callosum, there remain unresolved questions regarding its major patterns of variability. Although some sexual differences have been indicated by using traditional metric approaches (De LaCoste-Utamsing & Holloway, 1982; Holloway & de Lacoste, 1986; Holloway et al. 1993), there is no current agreement regarding whether or not such differences may be related to sexual variations, age differences or brain size (Allen et al. 1991; Jäncke & Steinmetz, 2003). Shape analyses using Jacobian determinant maps have confirmed sexual differences at the splenium in adults as well as through ontogeny, but without addressing the issues of covariation and allometry (Dubb et al. 2003).

In terms of evolution, shape and position of the corpus callosum are influenced by the general endocranial architecture, mainly by the flexion of the cranial base (Bruner & Jeffery, 2007), and non-human primates do not have the same pattern of variation described for our species (Holloway & Heilbroner, 1992). In humans, the intra-specific shape variation of the corpus callosum is very large, hampering robust statistical results when comparing inter-group differences. Within this framework, it must be assumed that the shape of the corpus callosum is influenced by intrinsic and extrinsic factors. The former are associated with fiber distribution and connectivity patterns between

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hemispheres. The latter are related to structural components of the brain–skull relationships. Therefore, the analysis of patterns of covariation underlying the observed shape variability might supply a quantitative tool for describing inter-group differences in terms of morphological integration and structural relationships.

Recently, we have analyzed the patterns of covariation in the midsagittal brain section of normal adult humans, to describe and quantify the underlying spatial relationships among the cortical and subcortical components (Bruner et al. 2010). Variability is largely due to fronto-parietal bulging of the cortical profile. We found a scarce integration between the cortical and subcortical elements and a limited allometric component, but some correlations between the posterior subcortical areas and the parietal contour. Males and females showed significant differences in size but not in shape of the midsagittal morphology, at least according to the configuration used in the study. In that analysis the corpus callosum was only represented by the position of genu and splenium. The major variation described at these areas was a size-related antero-posterior stretching of the corpus callosum length, due to the association between splenium and the anterior insertion of the tentorium cerebelli, caused by spatial proximity and consequent biomechanical relationships.

In the present paper we applied the same analytical framework to the morphology of the corpus callosum, to describe and quantify its midsagittal shape variation in a large sample of young adults, testing sexual variations against a null hypothesis of no differences according to within-group patterns of covariation.

Materials and methods

Magnetic resonance imaging midsagittal brain data were collected from a sample of 102 subjects, 57 females and 45 males, with the same age (mean age 19.5 and 20.3 years for females and males, respectively; total age range: 18–27 years – see Bruner et al. 2010 for details on sample and scanning). The shape of the corpus callosum was modeled by a configuration of 52 landmarks: the center of the genu; the center of the splenium;

and 50 semi-landmarks equally spaced along the corpus callosum outline, beginning from the posterior tip of the genu (Fig. 1). The configurations were registered by Procrustes superimposition, translating the coordinates systems to the same centroid, scaling the coordinates to unitary centroid size, and rotating the data so as to minimize the least-square residuals between corresponding landmarks (Bookstein, 1991). The residuals of the semi-landmarks along the outline were then further minimized through a sliding approach based on minimization of the bending energy values, as recommended for outlines and in particular for corpus callosum shape (Bookstein, 1997; Gunz et al. 2005). Centroid size is computed as the square root of the sum of squared distances of all the landmarks from their centroid. Coordinates were sampled by using *TPSDIG2* (Rohlf, 2005). Corpus callosum mean shape was averaged by using *TPSUPER* 1.14 (Rohlf, 2004). The shape variation was analyzed through principal component analysis and multivariate correlation on centroid size by using *MORPHOJ* 1.02h (Klingenberg, 2011), *MORPHEUS* (Slice, 1998) and *PAST* 2.08b (Hammer et al. 2001).

Results

Figure 2 shows the scree plot derived from the principal component analysis and the deformation grids for the first vectors. The multivariate shape space is not characterized by dominant components, but by a sequence of axes which variance decreases gradually. Broken stick approach computes the eigenvalues distribution under a random model (Jackson, 1993). Here, only the first five principal components show values above this threshold. Additionally, components explaining < 5% are often interpreted as noisy (or at least unstable) vectors (Jolliffe, 2002). Again, only the first five components are retained according to this criterion.

PC1 (29.8% of the total variation) is associated with dorsal bending of the corpus callosum and relative reduction of the splenium. PC2 (23.1%) is associated with antero-posterior stretching of the configuration and rotation of the splenium. PC3 (14.8) is associated with enlargement of the posterior areas. PC4 (8.7%) involves vertical compression of the genu and vertical stretching of the splenium. PC5 (6.1%) involves vertical stretching of the two extremities.

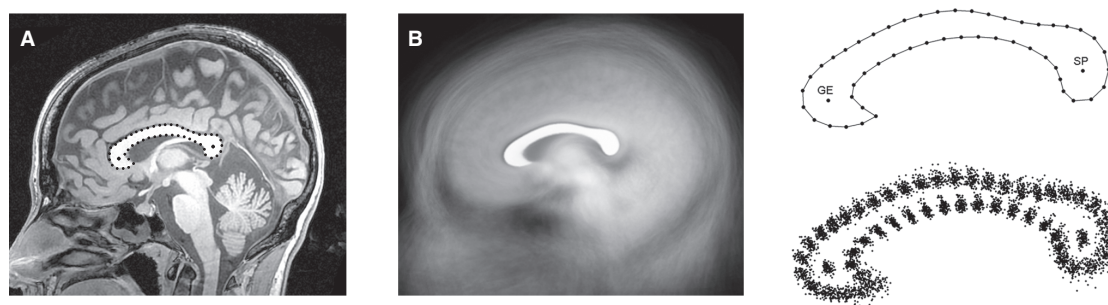


Fig. 1 The morphology of the corpus callosum was modeled by using the center of the genu, the center of the splenium, and 50 equally spaced semi-landmarks along the outline. Data were sampled on midsagittal magnetic resonance imaging section (A). The coordinates from 102 young adults were superimposed by Procrustes registration, by sliding the semi-landmarks according to a criterion of minimum bending energy (B). The superimposed image shows the corpus callosum mean shape computed as geometrical average of the whole sample.

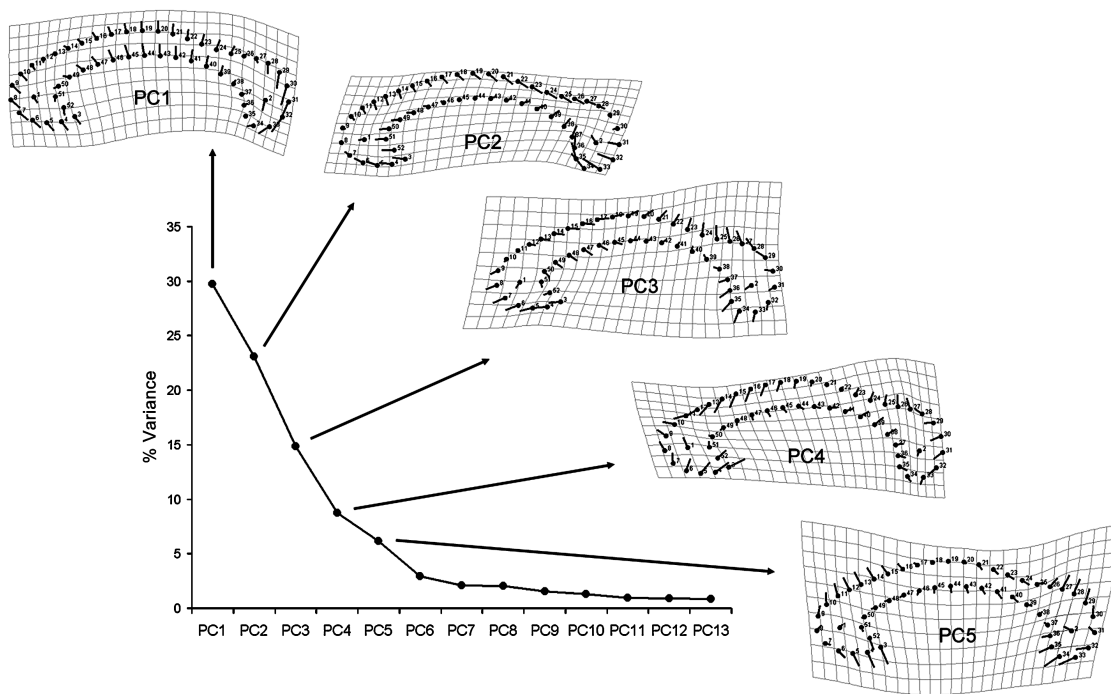


Fig. 2 The shape space is characterized by many significant principal components. The first five vectors explain more than 5% of the variance each. The thin-plate spline deformation grids show the geometrical changes along these axes.

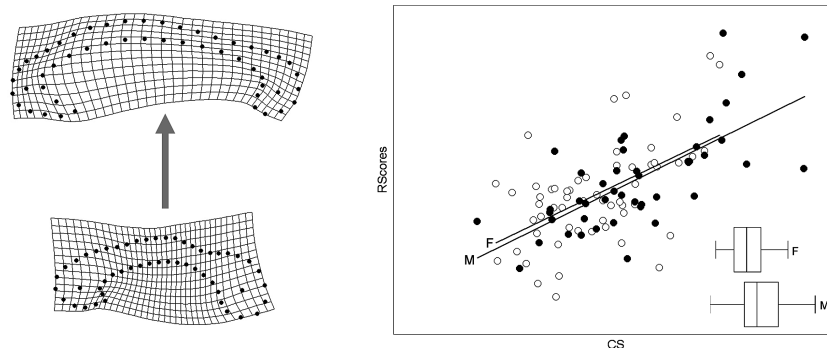


Fig. 3 Size explains 9% of the shape variance, involving from smaller to larger configuration (arrow) anterior–posterior stretching and relative reduction of the splenium. The plot shows males (black dots) and females (white dots) along this trajectory, according to their centroid size (CS) and their correlation score (RScores), with their group-specific least-square regression lines (M: males; F: females). At different scale, the non-parametric boxplots show the centroid size distribution for both sexes.

Males, on average, are of larger size than females (Mann–Whitney test, $P = 0.004$; Fig. 3), and they also appear to be more variable, even though differences in variance are not statistically significant (F -test, $P = 0.07$). Males show larger shape variation than females, mostly along the first two principal components.

Considering the whole shape variation, after discriminant analysis on the shape residuals differences between females and males involve (in the latter group) bending of the anterior half of the configuration (mostly at the genu) and relative reduction of the splenium. However, these differences

are not statistically significant ($P = 0.34$). Also a permutation test between males and females computed on Procrustes distances between groups shows no significant differences (1000 permutations, $P = 0.10$).

The allometric component (shape variation related to size variation) amounts to 8.8% ($P < 0.001$), and is associated with antero-posterior stretching of the configuration and relative reduction of the splenium (Fig. 3). This allometric vector is correlated with the first three principal components (PC1: $P = 0.01$, $r^2 = 0.07$; PC2: $P = 0.0001$, $r^2 = 0.18$; PC3: $P = 0.0001$, $r^2 = 0.15$). Within this allometric trajectory,

males and females show the same pattern, displaying the same slope ($P = 0.94$) and same adjusted mean value ($P = 0.59$) after analysis of covariance. Results do not change if regression is computed by using a pooled-within approach, that is using shape and size residuals according to the group-wise average. According to these results, shape variation due to the allometric component does not show sex-specific patterns, and it contributes little to the overall morphological variability. The null hypothesis cannot be falsified, and shape differences between males and female must be interpreted as being derived from size differences.

Discussion

The extreme morphological variation of the corpus callosum has been largely acknowledged since the earliest studies on this topic. This variability, together with the difficulties in quantifying its shape and in analyzing large samples, has hampered conclusive results concerning the normal variation of this subcortical element. In this geometric morphometrics approach, we analyzed the pattern of midsagittal shape variation of the corpus callosum in a large human sample. This sample included males and females of the same age. This is desirable because it removes the likely influence of age over corpus callosum morphology (Allen et al. 1991).

The principal component analysis computed here suggests that variations of the corpus callosum cross-section do not rely on strong patterns of integration. The more integrated a system, the more it relies on few dominant axes of covariation (Wagner, 1984; see also Bruner & Ripani, 2008). The lack of marked patterns of covariation underlies the large morphological variability of this element, explaining the difficulties in obtaining clear morphological signals and robust statistical evidence. The scarce integration might result from limited functional or structural relationships among the anterior, middle and posterior regions of the corpus callosum. Or, conversely, it may be associated with the influences of different extrinsic components. In fact, the corpus callosum contacts many cortical and subcortical areas, which are likely to influence its shape according to different functional and structural factors.

The allometric component is also very small, accounting for just 9% of the total shape variation. This small correlation between size and shape explains why shape differences between males and females are not significant, despite the recognizable size differences.

De LaCoste-Utamsing & Holloway (1982) proposed that females have a more bulbous and larger splenium. Analyzing the basic geometric configuration of the corpus callosum, Ozdemir et al. (2007) found some sexual differences in its posterior parts, but no differences in overall shape. It has been hypothesized that sex differences in the size of the corpus callosum may result from allometric variation, not from specific sexual characters

(Jäncke & Steinmetz, 2003). The size of the cross-section of the corpus callosum follows a geometrical rule when compared with the brain size in males and females. This means that the section enlarges at the power of two (a surface), the brain size at the power of three (a volume). Therefore, larger brains will have a relatively smaller corpus callosum cross-section. The present study confirms, on a quantitative basis, that females do have a relatively larger and more bulbous splenium in terms of shape. Nonetheless, at the same time, we evidenced that such minor differences result from size variation, not from sex-related characters. Hence, the current results support the hypothesis of scaling relationships between males and females, evidencing the role of the allometric pattern also for the shape component. It must be also noted that these shape differences at the splenium are part of a general longitudinal stretching involving the whole corpus callosum, associated with increasing size. The pattern described here by using the whole outline of the corpus callosum cross-section is in agreement with the one described using only the position of the genu and the position of the splenium in relationships to the other subcortical elements (Bruner et al. 2010).

We can provide three major conclusions regarding the morphological variation of the corpus callosum. First, it is very variable because of scarce integration among its parts, due to intrinsic or extrinsic factors. Second, there is a moderate allometric component showing that larger brains have a relatively smaller corpus callosum cross-section and relatively smaller splenium. Third, differences between males and females are secondary consequences of this allometric pattern, the former having mean larger size than the latter. The minor influence of the allometric component and the large variability associated with the scarce morphological integration make sexual shape differences negligible, obscured by individual components.

These results must be interpreted taking into consideration that this study, like many others, only concerns the midsagittal section of the corpus callosum. This section, because of its geometrical properties, is generally used as reference of a more complex three-dimensional system, which cannot be quantitatively analyzed through traditional metrics or landmark-based approaches. Although the form of the midsagittal section of the corpus callosum can provide useful information on the structural and functional organization of the brain, it must be properly interpreted just as a bi-dimensional layer joining two three-dimensional networks.

It has been hypothesized that morphological differences in the corpus callosum may underlie cognitive differences, influencing for example executive functions or even general intelligence because of intracortical and interhemispheric connectivity (Just et al. 2007; Hutchinson et al. 2009). It is likely that shape differences of the corpus callosum may be associated with intrinsic factors, like connectivity patterns

and volumes of the neural fibers. Nonetheless, they can be also the secondary consequences of extrinsic components, like the influence of pressures and tensions exerted by the surrounding cerebral elements. In both cases, a possible correlation between corpus callosum morphology and cognitive functions may be the direct result of neural configuration, as well as the indirect consequence of other kinds of spatial arrangements. Functional imaging and morphogenetic studies are required to evaluate these possibilities. Tractography might be particularly promising in this respect (Huang et al. 2005).

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