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ORIGINAL ARTICLE

Paracingulate asymmetry in anterior and midcingulate cortex: sex differences and the effect of measurement technique

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Abstract Many structural brain asymmetries accompany left hemisphere language dominance. For example, the cingulate sulcus is larger in the medial cortex of the right hemisphere, while the more dorsal paracingulate sulcus is larger on the left. The functional significance of these asymmetries is unknown because fMRI studies rarely attempt to localize activation to specific sulci, possibly due to difficulties in consistent sulcal identification. In medial cortex, for example, there are many regions of partial sulcal overlap where MRI images do not provide sufficient information to unambiguously distinguish a paracingulate sulcus from a displaced anterior cingulate segment. As large samples of postmortem material are rarely available for cytoarchitectural studies of sulcal variation, we have investigated the effect of variation in boundary and sulcal definition on paracingulate asymmetry in the MRI scans of 200 healthy adults (100 men, 100 women). Although women displayed a reliable asymmetry in the size of the paracingulate sulcus, regardless of boundary definition or technique, asymmetry was greatest when (1) the measurement was limited to the midcingulate region between the genu and the anterior commissure; and (2) the more dorsal of two overlapping sulci was always classified as a paracingulate sulcus (rather than as a displaced cingulate segment). The fact that paracingulate asymmetry is maximal in the midcingulate region suggests that this region may play a particular role in hemispheric specialization for language. Future work should investigate the structural and functional correlates of sulcal variation in this region.

Keywords Asymmetry · Cerebral cortex · Sex difference · Cingulate

Introduction

More cognitive functions have been attributed to the -anterior cingulate cortex than any other sector of the cerebrum (Devinsky et al. 1995; Bush et al. 2000; Rushworth et al. 2007; Rushworth and Behrens 2008). Functional imaging studies demonstrate activation during the assessment of complex information (Rushworth and Behrens 2008), generation of verbal category exemplars (Crosson et al. 1999), detection of conflict (Carter et al. 1999), pain modulation (Vogt et al. 2003), and selection of appropriate responses (Passingham 1996), while Price regards the region as "central to the … discussion of free will and discernment" (Price 2005), p. 136). Recent studies in monkey suggest that the anterior cingulate and orbitofrontal cortex play distinct roles in response selection. Cingulate cortex maintains a history of reward–*response* associations, while orbitofrontal cortex stores reward–stimulus associations (Rushworth and Behrens 2008).

Although authors generally pay tribute to the complex cytoarchitecture of the region, the averaging and smoothing employed in functional imaging studies rarely allow precise

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structure/function correlations. Activation attributed to the anterior cingulate cortex in group analyses is distributed over structurally and functionally distinct regions. Histology and connectivity vary with position in both the dorsoventral and rostrocaudal dimensions. Between the surface of the corpus callosum and the convexity, the cortex acquires a granular layer IV and prominent layer III pyramidal neurons (Table 1). In their pioneering study of this region, Vogt et al. determined that each of the cingulate subareas changed character in the region of the genu of the corpus callosum and used a prime to designate the region located between the genu and the anterior commissure (24a′… 32′) (Vogt et al. 1995). As a result of comprehensive cytoarchitectural and receptor architecture work, Vogt et al. have recently reaffirmed that the traditional Brodmann division of the cingulate cortex into anterior and posterior divisions should be replaced by a four region model consisting of anterior (24/32, mid (24′/32′), posterior (23/31) and retrosplenial (29/30) cingulate cortex (Vogt et al. 2003; Palomero-Gallagher et al. 2008a, b).

Accompanying the histological variation is considerable variability in sulcal morphology. The major sulcus in the region, the cingulate sulcus, can take an undulating and highly branched form (Fig. 1a), run relatively straight and unbranched close to the corpus callosum (Fig. 1b), or be segmented into several pieces (Fig 1c). The one landmark that allows unequivocal identification is the marginal ramus (MR) at the caudal end of the cingulate sulcus (Fig. 1). A second major sulcus, the superior cingulate or paracingulate sulcus, is frequently found dorsal to the cingulate sulcus (Smith 1907). Ono found that the superior cingulate sulcus formed a double parallel pattern (curving rostrally around the genu in parallel with the cingulate sulcus, as in Fig 2a, in both hemispheres of 6 of 25 brains examined postmortem (Ono et al. 1990). Later, authors used the term paracingulate sulcus and included shorter segments that did not curve around the genu (Paus et al. 1996b; Ide et al. 1999; Yucel et al. 2001). These authors found that the paracingulate sulcus was significantly more frequent in the left hemisphere than the right (see Table 2), while the volume of the cortex in the cingulate sulcus was, in contrast, larger on the right (Paus et al. 1996a).

The cortex on the medial surface of the frontal lobe forms a series of roughly concentric rings (Table 1) with area 24 closer to the corpus callosum than area 32. It is not clear how closely the boundary between histological areas 24 and 32 approximates the boundaries between cingulate and paracingulate sulcus. Eliot Smith felt that there were clear differences between cortex in the banks of the cingulate sulcus (area 24/24′) and more superior cortex (area 32/32′)—“the strip of cortex which is placed between the cingulate and paracingulate sulcus is often indistinguishable in structure from the part adjoining it on the other side of the paracingulate sulcus” (Smith, 1907, p. 250). Vogt et al. also reported that the presence of a double parallel pattern was associated with cytoarchitectural differences. When a second more superior sulcus was present, area 24c occupied the fundus of a relatively shallow cingulate sulcus and there was a corresponding expansion of areas 32 and 32′. When there was only one (cingulate) sulcus, areas 24 and 32 occupied the lower and upper banks of a markedly deeper cingulate sulcus (Vogt et al. 1995). But more recently, Palomero-Gallagher et al. declared that “although the paracingulate sulcus forms the outer limit of cingulate cortex, the adjacent gyrus is not the ‘para’ cingulate gyrus because it is part of cingulate cortex” (Palomero-Gallagher et al. 2008a, pp. 911–912). In support of this view, a cluster analysis performed on receptor data demonstrated that

Table 1 Brief summary of major structural trends in the dorsoventral and rostrocaudal dimensions of the anterior medial wall of the human cortex (Vogt et al. 1995; Vogt et al. 2003; Palomero-Gallagher, et al.2008a; Palomero-Gallagher et al. 2008b)

	Anterior cingulate—roughly anterior to genu of corpus callosum		Midcingulate—roughly posterior to genu of corps callosum	
Location	Area	Cytoarchitecture	Area	Cytoarchitecture
Subgenual	25	Poor laminar differentiation		
Within or near callosal sulcus	24a	Thin, undifferentiated layer III, Agranular layer IV; neuron sparse layer V	24a′	Large neurofilament expressing neurons, layer IIIc; Agranular layer IV, large neurons in layer Vb
Crown of cingulate gyrus	24b		24b′	
Ventral bank of cingulate sulcus	24c		24c′	
Dorsal bank of cingulate sulcus and more superior cortex	32	Dysgranular layer IV, large pyramids in layer III	32′	Dysgranular layer IV, larger layer III pyramids and fewer neurons in layer V than 32
	Receptor density significantly higher in 24/32		Receptor density significantly higher in 24′/32′	
Receptor	AMPA, Dopamine D1, $GABA_B$, α_2, Kainate, Benzodiazapine, M_3		$GABA_A$, NMDA	

*α2 n*oradrenergic alpha receptor, *M3* Muscarinic acetylcholine receptor

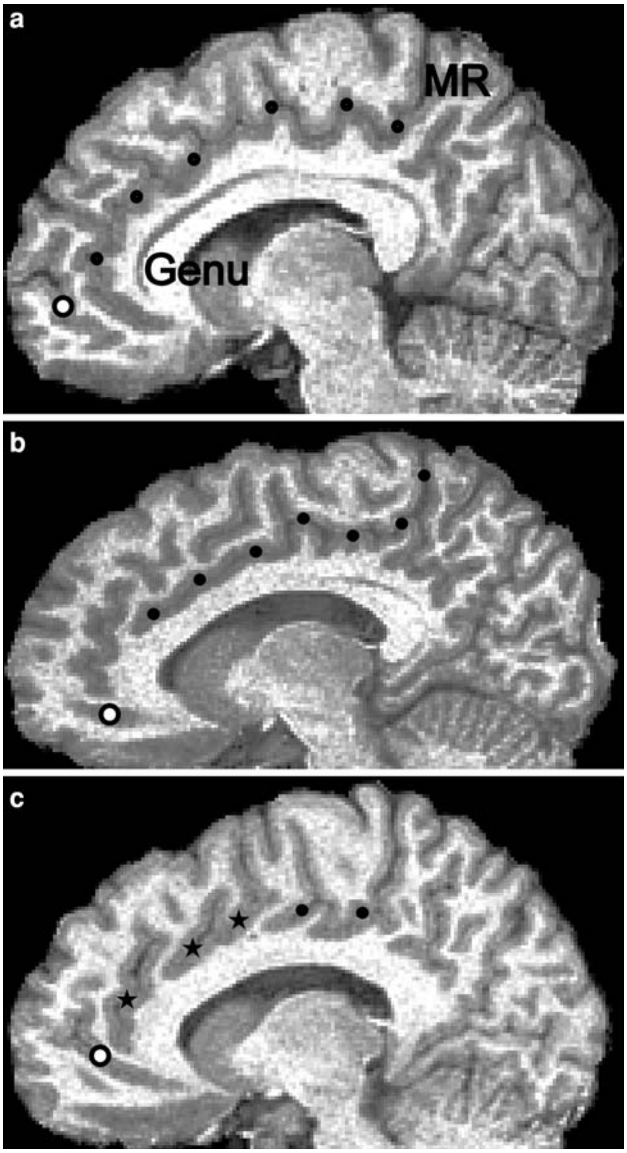

Fig. 1 Three examples of cingulate sulcus (*solid circles*) morphology. The superior rostral sulcus is indicated by *black edged circles*. **a** Undulating, highly branched cingulate sulcus sweeps forward from the marginal ramus (MR) and curves around the genu. **b** A cingulate sulcus with one branch at midpoint thins as it approaches the genu. **c** The cingulate segment that is attached to the marginal ramus terminates after its first branch. A series of short sulci of indeterminate identity (indicated by *stars*) cascades in the rostral direction. *Black rimmed circles* indicate the superior rostral sulcus

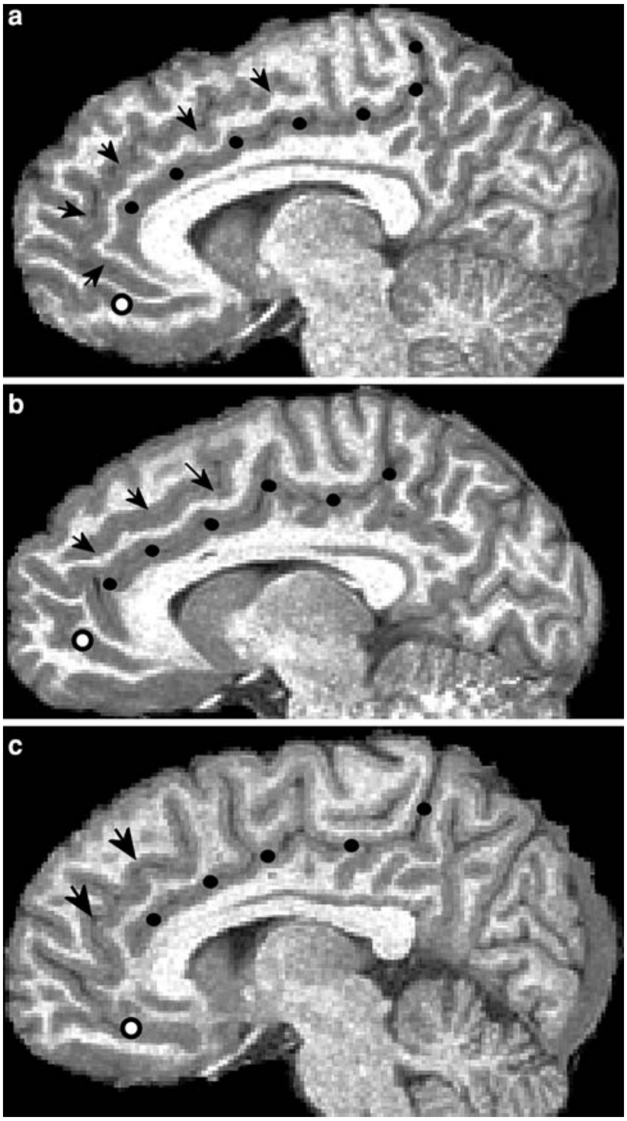

Fig. 2 Three examples of prominent paracingulate sulcus (*arrows*) morphology. **a** A long undulating paracingulate sulcus curves around the genu of the corpus callosum in parallel with a long unbranched cingulate (*solid circles*). **b** A long paracingulate sulcus is prominent but does not form a full double parallel pattern by curving around the genu. **c** A paracingulate sulcus that only partially overlaps the cingulate sulcus because the cingulate sulcus is short and terminates posterior to the genu. *Black rimmed circles* indicate the superior rostral sulcus

areas 24 and 32 are more similar to each other than they are to any of the other cytoarchitectonic areas on the medial wall (Palomero-Gallagher et al. 2008b).

Some functional imaging evidence supports the idea that there are important functional distinctions in the dorsoventral dimension. In an fMRI investigation that mapped activation to identified sulci in the midcingulate region, Crosson et al. (1999) found that the activation associated with the generation of category exemplars was located in the paracingulate sulcus, if this sulcus was present. In individuals without a paracingulate sulcus, the activation was found in the banks of the cingulate sulcus. Activation was never found on the crown of the cingulate gyrus (Crosson et al. 1999). This study, together with the evidence for a lateral asymmetry, mentioned above, suggests that the paracingulate cortex of the midcingulate region may be more closely involved in language generation than the more ventral regions. In support, a PET study that

Table 2 Summary of findings in previous studies of paracingulate sulcus asymmetry

Study/boundaries			Percent of cases		
			Absent	Present	Prominent
Paus et al. (1996b) 187 M, 60F	Group	Hemisphere		Vertical pieces	>2 cm long
No boundaries described	***	Left	8	38	54
No sex/hemisphere interaction		Right	15	48	37
Yucel et al. (2001) (103 M, 73F)				>2 cm long	>4 cm long
Anterior: junction with superior rostral; Posterior: Anterior commissure	M***	Left	17	25	58
		Right	36	33	30
	F	Left	39	25	36
		Right	40	35	25
Yucel et al. (2002) (75C, 55S)	C**	Left	16	23	61
All right handed males (controls from 2001 study)		Right	37	35	28
	S	Left	44	22	35
		Right	44	24	33
Le Provost et al. (2003) (100CM, 40SM)	C****	Left	34	14	52
All right handed males		Right	73	13	14
	S	Left	55	15	30
		Right	57	8	35

C control, *S* schizophrenia, *M* male, *F* female

Significant effect of hemisphere: ** $P < 0.01$; *** $P < 0.001$; **** $P < 0.0001$

mapped activation onto individual sulci in this region found that activation associated with the movements of the fingers was found in the cingulate rather than the paracingulate sulcus (Fink et al. 1997).

There is also some more indirect evidence that the lateral asymmetry in the frequency of the paracingulate sulcus has functional correlates. Two behavioral studies have reported that individuals with leftward asymmetry of the paracingulate sulcus performed better on tests of cognitive function than those with reversed asymmetry (Fornito et al. 2004; Fornito et al. 2006b). In addition, a functional imaging study in schizophrenia found that patients who lacked a paracingulate sulcus had less medial frontal activation (Artiges et al. 2006). Rightward asymmetry of more ventral cingulate gray matter, on the other hand, has been associated with harm avoidance in women (Pujol et al. 2002).

There is stronger evidence supporting a rostrocaudal differentiation between an "affective" anterior cingulate and a "cognitive" or "executive" midcingulate region (Vogt et al. 2003; Palomero-Gallagher et al. 2008a). Anterior cingulate cortex has connections with the amygdala, periacqueductal gray, and autonomic brainstem nuclei, while the midcingulate cortex has extensive connections with association cortex and projects to the skeletomotor and oculomotor systems (Devinsky et al. 1995; Picard and Strick 1996; Morecraft and Van Hoesen 1998). The presence of relatively few connections between the anterior and midcingulate regions further supports this functional distinction (Bush et al. 2000).

Several structural MRI studies have investigated whether paracingulate asymmetry varies as a function of sex or behavioral diagnosis. Most of these studies have used a qualitative three category system originated by Paus et al. (1996b). Although all studies applied the same three category names (prominent, present, and absent) the sulcal forms included in these categories vary somewhat. Figure 2b gives an example of a paracingulate sulcus that would be rated *prominent* in all systems. Figure 2c, by contrast, gives an example of a paracingulate sulcus that would be rated *prominent* in the Paus, but *present* in the Yucel system because the overlapping segment is less than 4 cm long.

Figure 3 provides three further examples of paracingulate sulci that would be rated *present* in the Yucel system. These examples illustrate how the length and boundary criteria divide a continuum of sulcal patterns into arbitrary categories. Figure 4 provides examples of another sulcus in medial cortex, the intralimbic sulcus. This sulcus is described as a secondary sulcus (although not named) by Vogt et al. (1995) and as a shallow sulcus between the cingulate sulcus and the corpus callosum by Paus et al. (1996b). When this sulcus is long and deep, it can pose classification difficulties.

In spite of the difference in criteria and boundary conditions and ambiguities in sulcal identification, the results

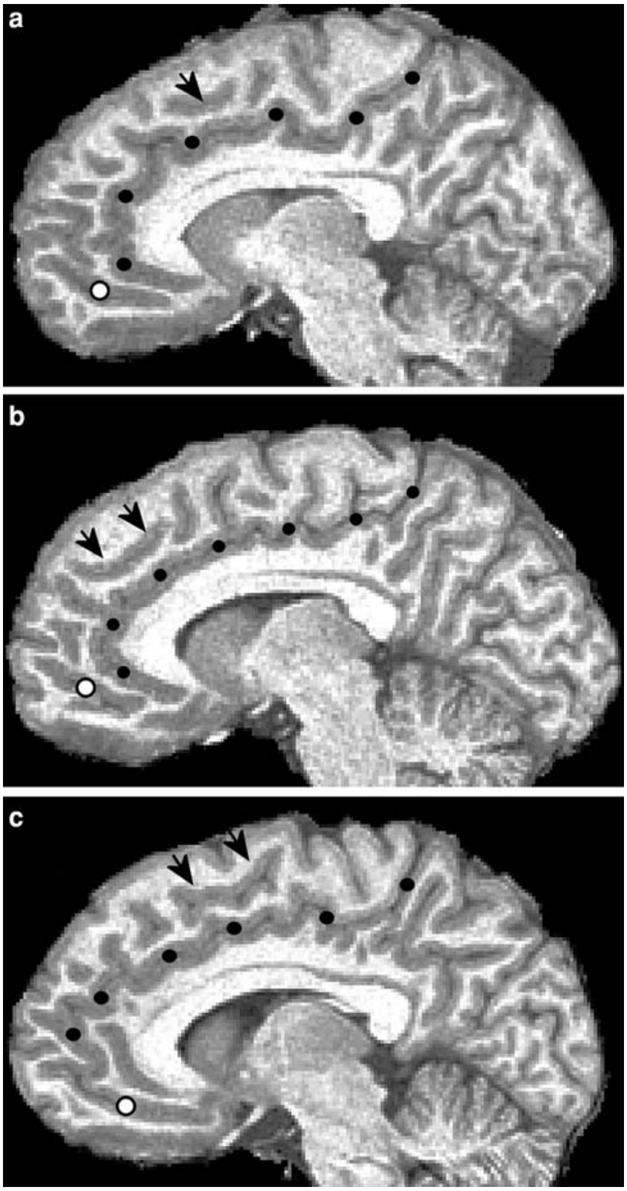

Fig. 3 Three examples of present paracingulate sulcus (*arrows*) morphology. **a** A short flat sulcus about 2.5 cm long. **b** A paracingulate sulcus that is close to the boundary between present and prominent. **c** A paracingulate sulcus longer than 4 cm is rated present rather than prominent because it crosses the anterior commissure plane into the posterior cingulate compartment (indicated by *caudal arrow*)

of published studies have been roughly consistent (see Table 2). Over all studies using the three category system, the paracingulate sulcus has been rated

1. *Prominent* in a majority (52% to 61%) of left hemispheres.
2. *Absent* in 8% to 34% of left hemispheres.
3. *Prominent* in 14% to 37% of right hemispheres.
4. *Absent* in 15% to 73% of right hemispheres.

In contrast to the results in men, only a third of the left hemispheres of women (one study) (Yucel et al. 2001) and patients with schizophrenia (two studies) (Yucel et al. 2002; Le Provost et al. 2003) have *prominent* paracingulate sulci. The Paus study found that the paracingulate sulcus was *absent* or *prominent* more often in women than men regardless of hemisphere (Paus et al. 1996b).

In addition to the studies listed in Table 2, two studies have used quantitative methods to investigate sex differences in paracingulate asymmetry. Paus et al. found no sex difference in asymmetry (Paus et al. 1996a) while Huster et al. found an interaction between sex and hand preference. Male right handers and female left handers had a significant leftward asymmetry while female right handers and male left handers did not (Huster et al. 2007). To summarize, studies of right handers are split. Two studies report similar levels of asymmetry in the two sexes and two others report that women lack paracingulate asymmetry.

We wondered if some of the reported variability in paracingulate frequency might be attributable to variability in boundary conditions and the classification of intermediate morphological forms (Figs. 4, 5, 6). In Fig. 4c, there are two long sulci running parallel to the corpus callosum. It is unclear whether the sulci are an intralimbic (area 24a) and a cingulate sulcus (area 24c) or a cingulate and a paracingulate sulcus (area 32). Figure 4d demonstrates another interpretational problem. Here, the sulcus closest to the corpus callosum could be a rostral continuation of the posterior cingulate sulcus, or an intralimbic sulcus ventral to the cingulate sulcus.

Figure 5 shows examples of another intermediate form—*overlap*. In these hemispheres, the sulcus that is attached to the marginal ramus (the cingulate sulcus proper) fails to curve ventrally around the genu. A second sulcus that curves around the genu overlaps the more ventral cingulate sulcus for a variable extent. The identity of this second sulcus is ambiguous. In the overlapping region, it fits the criteria for a paracingulate sulcus, in that it is dorsal and parallel to the cingulate sulcus. In the perigenual region, however, it fits the criteria for the rostral part of an interrupted cingulate sulcus, the designation given by Ono et al. (1990, Fig. 13.1D). The Yucel group also calls these formations interrupted cingulate sulci, but identifies the more ventral sulcus as the cingulate sulcus and the more dorsal sulcus as the superior cingulate sulcus (A. Fornito, private communication). When the superior cingulate sulcus overlaps the cingulate sulcus by more than 2 cm, it is classified as a *present* paracingulate sulcus (Fig. 5b) and when the overlap exceeds 4 cm, it is classified as a *prominent* paracingulate sulcus (Fornito et al. 2006a). Examples of another intermediate form called *pieces* because more than one sulcus has an ambiguous identity are shown in Figure 6. The cytoarchitectural and functional correlates of such formations are unknown but they present a challenge for qualitative classification systems.

We had the opportunity to investigate the asymmetry of the cingulate and paracingulate sulci in a sample of 200 healthy young adults who received MRI scans in a study of behavioral and anatomical asymmetry (Chiarello et al. 2009a, b; Leonard et al. 2008). Our major concern was how lateral asymmetry in men and women would be affected by the use of different techniques and classification decisions on hemispheres with intermediate forms. We compared two anterior boundary conditions (see Fig. 7): the anterior boundary described by Yucel (where there is an inflection point in the slope of the sulcus) and the anterior border of the genu (to approximate the anterior border of midcingulate cortex (Vogt et al. 2003)). We asked the following questions:

1. (a) How does the inclusion of additional categories such as “overlap” and “pieces” affect the frequency distributions in the two hemispheres? (b) Is there a sex difference?
2. (a) Does classifying overlapping sulci as paracingulate sulci (following the Yucel group convention) produce asymmetries similar to those reported in the literature? (b) Is there a sex difference?
3. (a) Does a continuous measure of degree of overlap demonstrate a lateral asymmetry? (b) Does choice of anterior boundary affect the asymmetry? (c) Is there a sex difference?
4. (a) Is there an inverse correlation in the gray matter volumes in the cingulate and paracingulate sulcal banks as suggested by Vogt et al. (Vogt et al. 1995)? (b) Does this correlation differ in the anterior and midcingulate regions? (c) Is there a sex difference?

Method

Subjects

Brain imaging and selected demographic data were collected on 100 men and 100 women recruited from a university community. The study was approved by ethics committees (Institutional Review Boards) at both the University of California and the University of Florida. Subjects with a history of brain injury or disease or conditions incompatible with an MRI scan were excluded. Four subjects who reported meeting these criteria were subsequently excluded for incidental findings on the magnetic resonance imaging (MRI) scan. The MRI scans were obtained on a 1.5-T GE scanner (3-D SPGR, 1.2 mm thick sagittal images) in a GE Signa 1.5 Tesla Scanner. Imaging

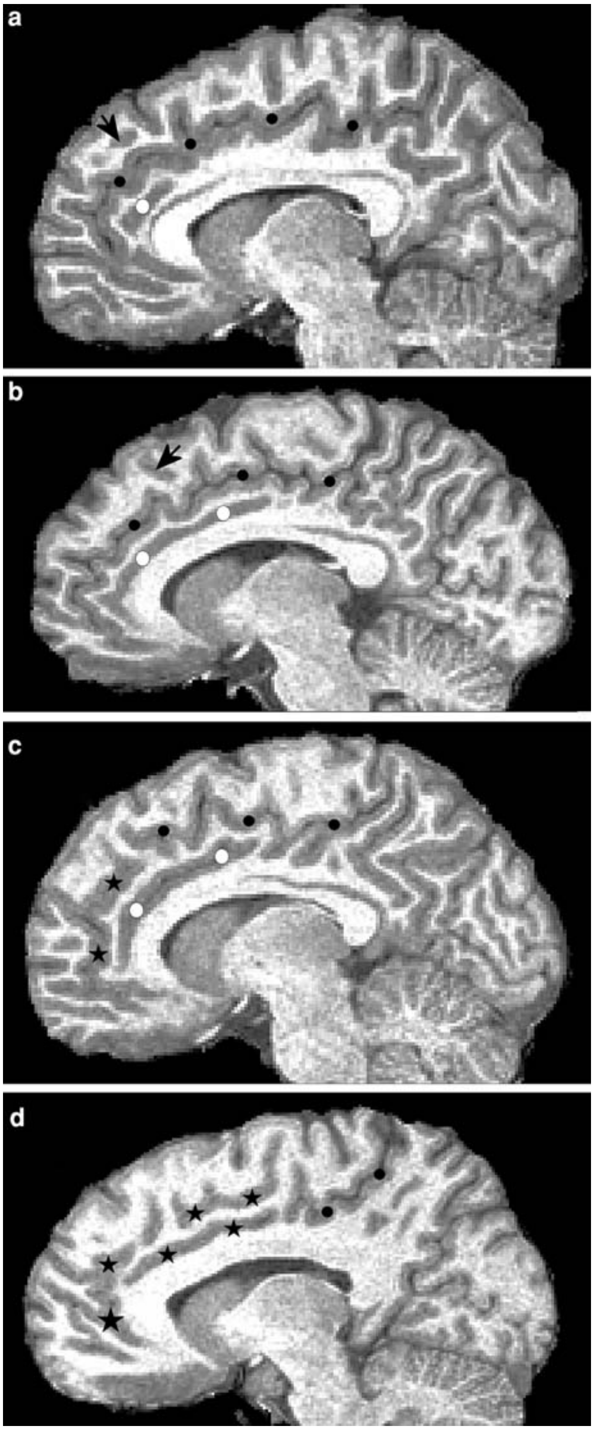

Fig. 4 Four examples of unbranched pericallosal sulci of varying extent. **a** Typical shallow secondary intralimbic sulcus (*white circle*) and more dorsal uninterrupted cingulate sulcus (*solid circles*). **b** Longer but still shallow intralimbic sulcus and uninterrupted cingulate sulcus. **c** Long, deep sulcus of indeterminate identity, short posterior cingulate sulcus (*solid circles*, and ambiguous anterior sulcus (*stars*). **d** Unbranched sulcus that appears to be a rostral continuation of the posterior cingulate sulcus. (i.e., an anterior cingulate segment) Using the classification system described in the text, the more dorsal sulci (*stars*) would be classified as segments of a paracingulate sulcus

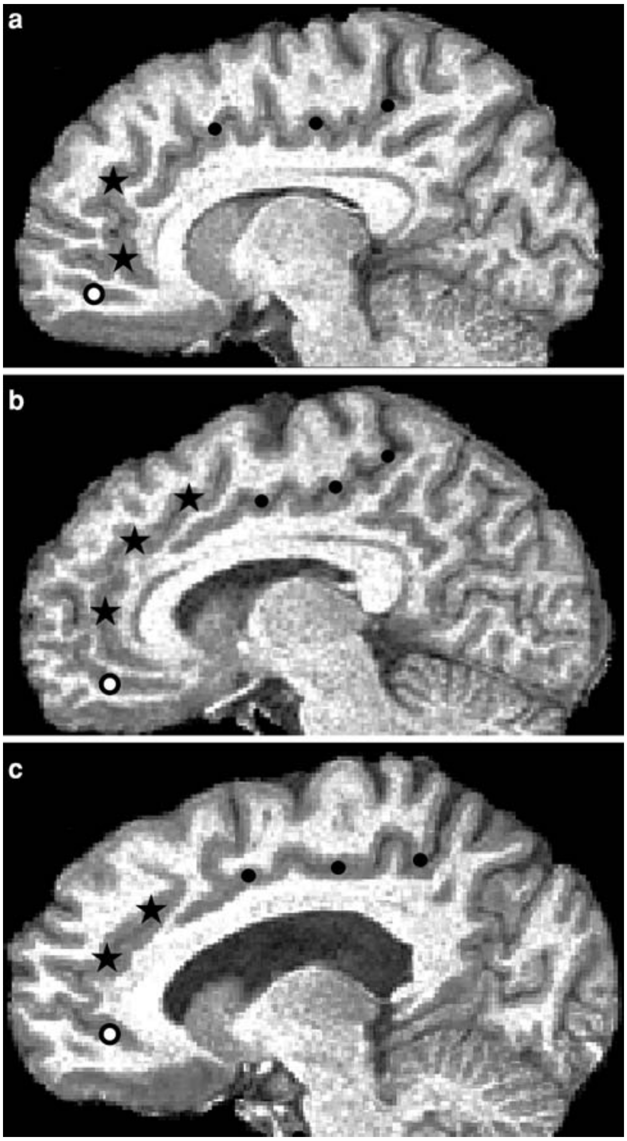

Fig. 5 Three examples of ambiguous paracingulate morphology rated overlap in the present study. The cingulate sulcus (*solid circles*) terminates caudal to the genu. *Black rimmed circles* indicate the superior rostral sulcus. The anterior, partially overlapping sulci in each example are indicated by *stars* because they share characteristics with both an anterior segment of the cingulate sulcus and a paracingulate sulcus. When this type of formation was classified as *absent* in this study, the expected leftward asymmetry in paracingulate frequency was not found because the category *absent* became more prevalent in the left than right hemisphere

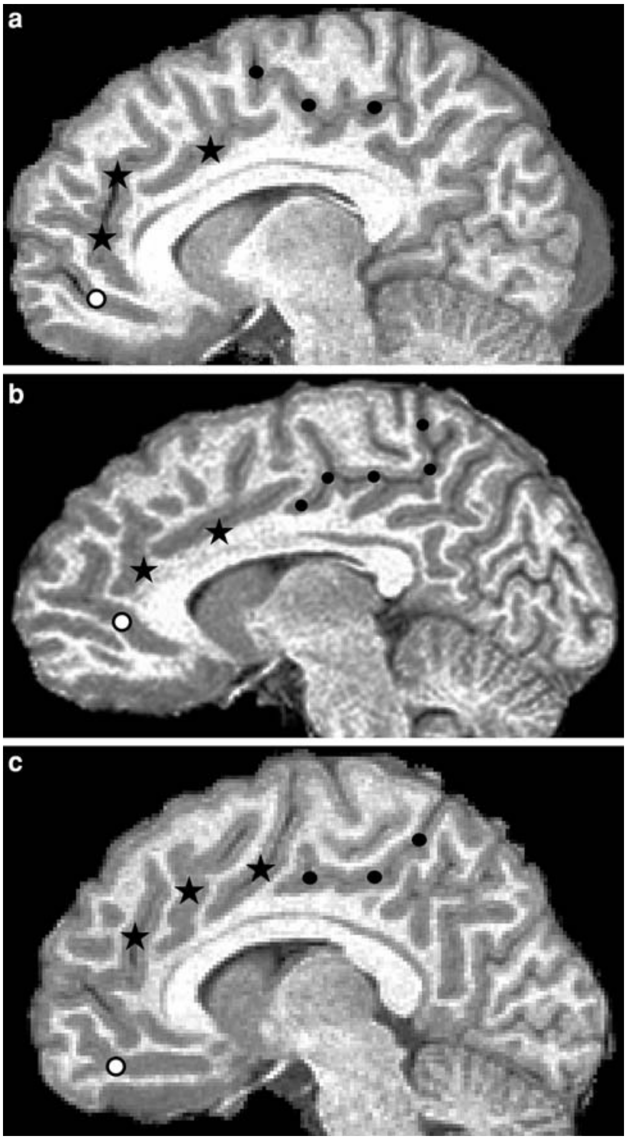

Fig. 6 Three examples of formations rated pieces due to the presence of more than one indeterminate sulcus. **a** Posterior cingulate segment (*solid circles*) a short sulcus (*star*) and a perigenual sulcus (*star*). **b**. Posterior cingulate segment (*solid circles*), short unbranched sulcus that could be an intralimbic sulcus (*star*) and a short anterior sulcus (*star*). **c** A cascade of sulci (*stars*) are oriented vertically rather than parallel to the corpus callosum. *Black rimmed circles* indicate the superior rostral sulcus

parameters: TR 11 ms; TE 2.2 ms; flip angle, 25°; field of view, 24 cm; acquisition time, 4.36 min.

The men and women did not differ in mean age (21.7 ± 3.7 vs. 21.5 ± 3.3 years), parental education (3.40 ± 1.03 vs. 3.25 ± 1.06 with five representing a professional degree), hand preference (+0.67 ± 0.54 vs. +0.74 ± 0.52 (1 = completely right handed)) (Bryden 1982), Passage Comprehension percentile (67.9 ± 22.4% vs. 63.0 ± 23.4%) (Woodcock 1987) or short form estimates of Verbal (108.7 ± 11.2% vs. 108.8 ± 10.8%) and Performance (110.3 ± 11.4 vs. 107.3 ± 11.3) IQ (Wechsler 1997) (although, it should be noted that sex biased questions are dropped during construction of these tests (Halpern et al. 2007)). All were native speakers of English with normal or corrected-to-normal vision. Fifteen men and 13 women in this sample wrote with their left hand. As the number of left handers in the sample provided inadequate power for testing the presence of the sex hand

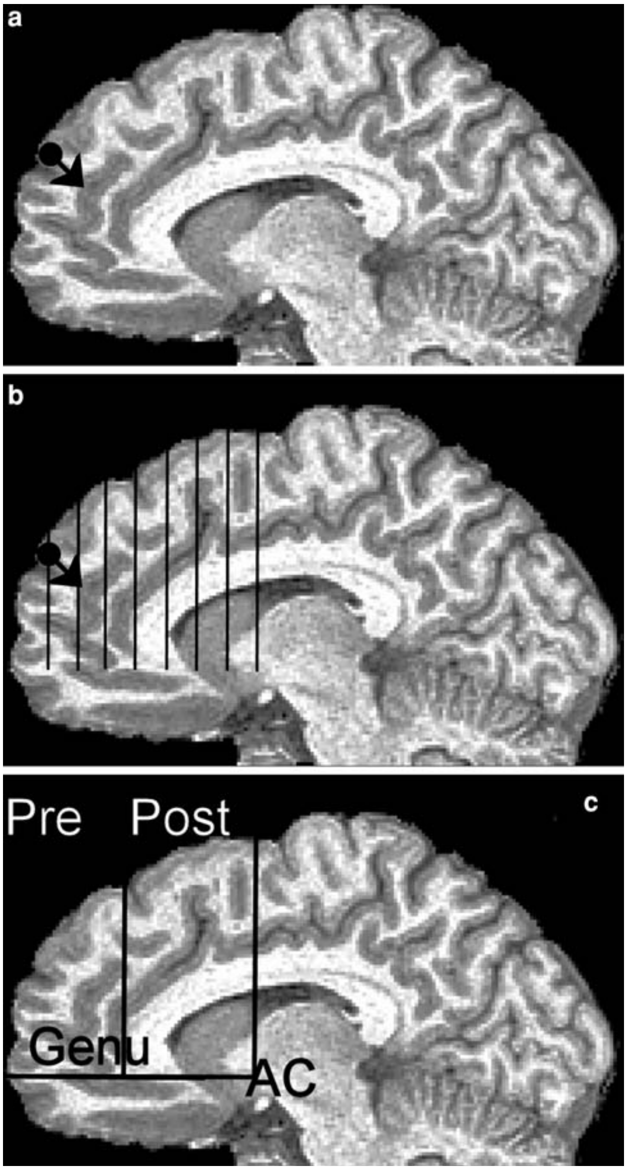

Fig. 7 Boundaries used in different methods. **a** *Arrow* indicates the imaginary vertical line where the course of the paracingulate changes from dorsoventral to rostrocaudal. This is the anterior boundary used by Yucel et al. (2001). **b** *Vertical lines* separated by 1 cm intervals mark the columns used for length estimation in this study. Posterior boundary is the anterior commissure (AC). **c** *Horizontal and vertical lines* designating the pre (putative anterior cingulate) and postgenual (putative midcingulate) compartments used for gray matter volume estimation in this study

interaction described in Huster et al. (2007) all analyses were repeated with and without the presence of the left handers (see below).

Image processing

The images were reviewed for neuropathology by a neuroradiologist (R.O.) and then transferred to compact discs at the Imaging Center and sent to the McKnight Brain Institute at the University of Florida. Image preprocessing was performed with FSL scripts (http://www.fmrib.ox.ac.uk/) (Smith et al. 2004). Extraction of the brain parenchyma from scalp and skull was performed with BET (Smith 2002) before registration (FLIRT) (Jenkinson and Smith 2001) to a 1 mm isovoxel study-specific template image aligned into the Talairach planes. No warping was performed on the images. Segmentation into separate gray matter, white matter, and cerebrospinal fluid (CSF) volumes was performed using FAST (Zhang et al. 2001). In these volumes, each voxel is represented as a partial volume estimate of a particular tissue type. The volume of each tissue type was calculated by multiplying the number of voxels times the average partial volume estimate of those voxels as described on the FSL website. Measured values were automatically accumulated in a data file for statistical analysis. All assessments were made blind to individual characteristics and hemisphere laterality using scripts written in PV wave. We used three methods to assess cingulate morphology: qualitative categorization, length estimation, and gray matter volume estimation. All measurements were made blind to hemisphere and subject characteristics.

Qualitative categorization

Almost all studies of cingulate morphology have employed three categories: *prominent*, *present*, and *absent* with the criteria and boundaries for these categories varying somewhat from study to study. For example, Yucel et al. (2001) reduced the ambiguity in anterior regions by ignoring the part of the paracingulate sulcus that curved ventrally around the genu (see arrow in Fig. 7).

Qualitative categorization was performed on each hemisphere after paging through adjacent sections to evaluate sulcal continuity. We used the Yucel group's criteria for defining the paracingulate as *prominent*, *present* or *absent*, but instead of folding interrupted overlapping cingulate sulci into the same categories, an additional category *overlap* was created. The paracingulate sulcus was defined as *prominent*, if the cingulate sulcus crossed the vertical plane of the genu and a second sulcus overlapped the cingulate sulcus for more than 4 cm (lengths were adjusted for brain size). The paracingulate was defined as *present* if the cingulate reached the genu and a second sulcus overlapped the cingulate sulcus for more than 2 cm. The paracingulate was rated *absent* if the total length of horizontal pieces dorsal to the cingulate sulcus was less than 2 cm. *Overlap* was used when the sulcus closest to the corpus callosum (putative cingulate) did not extend to the vertical plane of the genu and a second sulcus that did cross this vertical boundary appeared more dorsally (Fig. 5). The category *pieces* was used (as a last resort) when there were more than two sulci whose identity was ambiguous (Fig. 6).

Length estimation

On a midline image, the coordinates for horizontal and vertical lines marking the perpendicular planes passing through the anterior commissure were located. These coordinates were then used to paint vertical and horizontal lines on a sagittal image chosen so that its lateral position was 10% of the distance to the lateral edge of the hemisphere ($x =$ approximately 7 Talairach mm). (Preliminary analyses determined that although sulcal morphology was clearest at this distance from the midline, results were comparable when images 6 or 8 Talairach mm from the midline were used.) The sagittal image was rotated clockwise 10° in order to bring the dorsal surface of the corpus callosum (and, as a consequence, the sulci to be classified) into the horizontal plane. This rotation increased the amount of overlap in the horizontal plane. A series of vertical lines separated by 1 cm intervals then appeared between the anterior commissure and the frontal pole (Fig. 7b). Length estimates were made by counting the intervals containing two parallel and overlapping sulci. No attempt was made to identify the participating sulci as either cingulate or paracingulate sulci. These counts were automatically entered into a text file. Two counts were made. The first used the Yucel group's criterion for the anterior boundary (when the axis of the paracingulate sulcus changes from vertical to horizontal) (Yucel et al. 2001). The second count used the genu of the corpus callosum as a proxy for the border between anterior and midcingulate regions (Bush et al. 2000; Vogt et al. 2003).

Gray matter volumes

Gray matter volumes of the sulcal components were measured by (1) outlining the more ventral and the more dorsal sulcus in the anterior cingulate (pregenual) and midcingulate (postgenual) regions on a sagittal image 6 to 9 mm from the midline (chosen to maximize gray/white contrast). This mask was then applied to all the adjacent sagittal images that contained both gray and white matter (as identified in the partial volume estimate files created by FAST). Because of the ambiguity in sulcal identification described above, the cingulate measurement contained all gray matter in the sulci closest to the corpus callosum (except in the case where there was an intralimbic sulcus ventral to a continuous (Fig. 4a, b) or clearly segmented (Fig. 4c) cingulate sulcus). The paracingulate measurements contained all gray matter that was separated from the corpus callosum by a sulcus. In the case of partially overlapping sulci, these decisions led (as in the linear estimates above) to the paradoxical result that cortex classified as cingulate in the pregenual region was continuous with cortex classified as paracingulate in the postgenual region (see Fig. 8).

Statistical analysis

Data were automatically entered into text files, imported into spreadsheets, and analyzed with PC-SAS (SAS 2007). Qualitative analysis: Chi square analysis was performed to determine the effect of hemisphere in the entire sample and then separately in the men and the women. Quantitative analyses: The paracingulate length estimates were increased by 1 and volume values were log transformed to remove zeros and improve normality. Analyses of variance with two factors (side and sex) and an interaction term were used to assess the degree of lateralization in the two sexes. The volume of hemispheric gray matter volume was added as a covariate to control sex differences in cerebral volume. Post hoc t tests were conducted when the interaction effect reached a significance level below $P < 0.05$. Pearson correlation coefficients were calculated to measure the degree of association between the volumes of cingulate and paracingulate gray matter. All analyses were repeated without the inclusion of the individuals who wrote with their left hand. As removing the left handed individuals decreased the significance levels slightly and inspection of

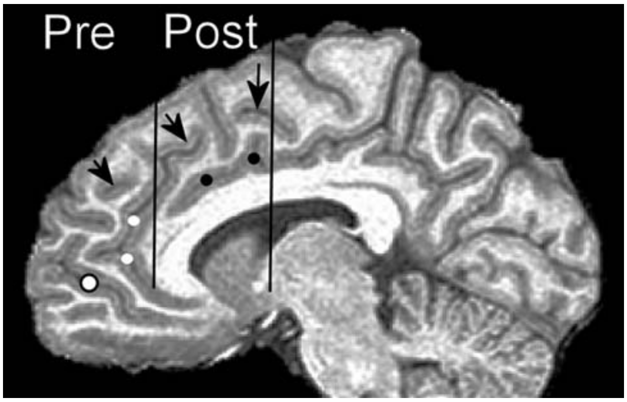

Fig. 8 Illustration of method used to characterize ambiguous sulci for length and gray matter volume measurements. *Vertical lines* mark the anterior commissure and genu landmarks which were located on the midsagittal plane. A *black rimmed circle* indicates the superior rostral sulcus. In the postgenual compartment (Post), the cingulate sulcus is indicated by *solid circles* and the paracingulate by *arrows*. In the pregenual compartment (Pre), the "cingulate sulcus" (which is continuous with the "paracingulate" sulcus in the postgenual compartment) is marked by *white circles* to indicate its hybrid nature. A more dorsal sulcus (*arrow*) is measured as paracingulate in the pregenual compartment. This counterintuitive method produces the expected leftward asymmetry for "paracingulate" in the postgenual compartment and the expected rightward asymmetry for "cingulate" in the pregenual compartment

the data demonstrated no consistent effect of hand preference, the results of analysis of the entire sample are reported.

Results

Question 1 (a) Is there a lateral asymmetry in the distribution of the paracingulate sulcus when five categories (including overlap and pieces in addition to prominent, present, and absent) are used for classification?

The distribution of the five categories is presented in Table 3. Chi square analysis demonstrated a highly significant lateral asymmetry ($\chi 2$ (4) = 24.95, $P < 0.0001$). Sixty percent of prominent and overlapped sulci were found in the left hemisphere, while the categories *pieces*, *present*, and *absent* were more characteristic of the right hemisphere. If regions of overlap are not classified as *prominent* paracingulate sulci as was done by Fornito et al. (2006a), the hemisphere asymmetry is greatly diminished.

Question 1(b) Is there a sex difference in these distributions?

The distribution of the five categories is graphed separately for men and women in Fig. 9. Most surprisingly, men showed no lateral asymmetry while the difference in the distributions in the two hemispheres in women was highly significant ($P < 0.0001$). Women had twice as many *prominent* and *overlapped* and half as many present sulci in the left hemisphere as they did in the right hemisphere. In the men, the distributions of paracingulate types were much more comparable in the two hemispheres. This sex difference was due to the distribution of paracingulate categories in the right, not the left hemisphere. The men had twice as many *overlapping* and *prominent* paracingulate sulci in the right hemisphere as the women ($\chi 2$ (4) = 15.1, $P < 0.01$), while there was no sex difference in the distributions in the left hemisphere ($P > 0.50$).

This result is inconsistent with all four previous studies of right handers. These previous studies either failed to find a sex difference (Paus et al. 1996a; Paus et al. 1996b), or found a greater degree of asymmetry in men (Yucel et al. 2001; Huster et al. 2007).

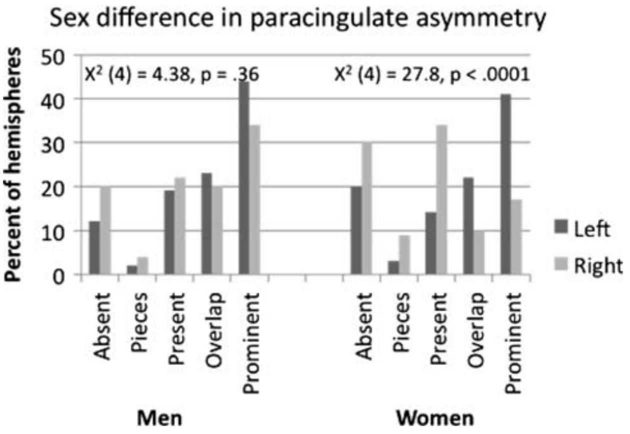

Fig. 9 Histograms of the distribution of paracingulate types in 100 men and 100 women when five categories were used for classification. The distributions in the left and right hemispheres of men were not significantly different. In contrast, in women, the frequencies of *prominent* and *overlap* were greater in the left than the right hemisphere while the frequency of present was greater in the right than the left hemisphere

Question 2 (a) Does merging *overlap* and *pieces* with the original three categories produce distributions that resemble those reported in the literature? (b) Is there a sex difference?

We hypothesized that one reason our results differed so strikingly from previous research was that our five category system led to misclassification. We therefore repeated the assessment, using the traditional three categories. Formations previously rated *overlap* were classified as either *present* or *prominent* based on the length of the overlap (Fornito et al. 2006a). Hemispheres with short sulci that had been classified as pieces were now classified as *absent*. Table 4 presents the results. Although the percentage of *prominent* increased in the left hemispheres of both men and women the asymmetry was much more marked (and significant) in women ($\chi 2$ (2) = 26.23, $P < 0.0001$) than men: $\chi 2$ (2) = 5.37, $P = 0.068$).

Table 3 Initial qualitative analysis with five categories of cingulate/paracingulate morphology in 200 healthy young adults

		Percent of hemispheres				
	Hemisphere	Absent	Pieces	Present	Overlap	Prominent
$N = 200$	Left****	16	3	17	22	42
	Right	25	7	28	15	25

**** Significant effect of hemisphere (chi square analysis), $P < 0.0001$

Table 4 Qualitative analysis with three categories in men and women (*M*: male; *F*: female)

Qualitative	Side	Absent	Present	Prominent
Male	Left	18	29	53
$N = 100$	Right	32	22	46
Female****	Left	26	23	51
$N = 100$	Right	57	24	19

**** Significant effect of hemisphere (chi square analysis), $P < 0.0001$

Table 5 Length analysis of the paracingulate sulcus using two different boundary conditions in men and women (*M*: male; *F*: female)

	Boundary	Yucel		Genu	
Sex	Hemisphere	Mean	SD	Mean	SD
M	Left	2.14	1.51	1.61^{+}	.94
	Right	1.87	1.47	1.3	.9
F	Left	1.84****	1.37	1.6****	1.06
	Right	1.06	1.24	0.81	0.83

	df	*F*	*P<*	*F*	*P<*
Overall	3,396	10.54	0.0001	11.96	0.0001
Hemisphere		13.65	0.001	21.02	0.0001
Sex		11.62	0.001	10.25	0.01
Interaction		6.34	0.05	4.61	0.05
Amount of variance explained		7%		8%	

For the statistical analysis the values were increased by one and log transformed to increase normality

Significant effect of hemisphere **** $P < 0.0001$, $^{+}P = 0.08$ (post hoc Bonferroni corrected *t* test)

Given difficulties encountered in fitting what appeared to be a continuous, even multidimensional, distribution without sharp or meaningful boundaries into three categories, the assessment was repeated several times. Although the individual ratings were not acceptably reliable (intra and inter rater intraclass correlations coefficients in the 60 to 70% range), the distributions in repeated assessments differed by only a few percentage points and the hemispheric distribution in the men continued to resist the significance barrier. When the repeatability of the classifications was examined in the two sexes separately there was no difference in repeatability between the sexes.

Question 3 (a) Does a continuous measure of overlap demonstrate a lateral asymmetry? (b) Does choice of anterior boundary affect the asymmetry? c) Is there a sex difference?

Length analysis

Dissatisfaction with squeezing a continuous distribution into categories drove the development of a more quantitative approach. As described in the methods section, a grid of 1 cm columns was superimposed on a sagittal image (Fig 7b) and the number of columns that contained two overlapping sulci regardless of sulcal identity was determined. Table 5 presents the results. Two different anterior boundaries were used, the one described in Yucel et al. (2001) and the anterior border of the genu. The results were remarkably consistent with those from the previous categorical assessment. Once again, women, but not men, had a highly significant lateral asymmetry. Although only a small amount of variance was explained, the sex/hemisphere interaction was significant with either boundary. The effect sizes (Cohen 1977) of the paracingulate asymmetry were larger, in both sexes, however, when measurement was more limited to the midcingulate region (genu of the corpus callosum as the anterior boundary) (women: Yucel boundary: Cohen's $d = 0.6$; genu boundary: $d = 0.83$; men: Yucel: $d = 0.18$; genu: $d = 0.33$).

Volumetric analysis

The volumes of the ventral (cingulate) and dorsal (paracingulate) members of overlapping pairs of sulci were measured separately in the pregenual and postgenual compartments as demonstrated in Figure 8. Table 6 shows the results of all four regional analyses. For the cingulate sulcus, the component in the anterior cingulate (pregenual) but not the midcingulate (postgenual) regions showed the expected rightward asymmetry and the effect of the gray matter covariate was significant, particularly in the anterior cingulate (pregenual) region. For the paracingulate sulcus, both anterior cingulate (pregenual) and midcingulate (postgenual) components demonstrated a significant leftward lateral asymmetry and the effect of the gray matter covariate was not significant. The fact that the gray matter covariate was significant for the cingulate but not the paracingulate cortex means that cingulate but not paracingulate volume is correlated with gray matter volume. Additional analyses showed that the volume of midcingulate cortex in the left but not the right hemisphere correlated with gray matter volume in both men and women (women: Pearson $r = 0.32$, $P < 0.01$; men: $r = 0.34$, $P < 0.001$). For anterior cingulate cortex, the only significant correlation was in the right hemisphere of men ($r = 0.27$, $P < 0.01$).

Both men and women demonstrated a significant leftward asymmetry for paracingulate sulcal volumes in the midcingulate (postgenual) region and a significant rightward asymmetry for cingulate volumes in the anterior (pregenual) region. There was a significant sex–hemisphere interaction for paracingulate volumes in the midcingulate (postgenual) region because women had smaller volumes in the right hemisphere than men. There was also a significant sex–hemisphere interaction for cingulate volumes in the anterior cingulate (pregenual) region because (after correction for gray matter volume) the men had smaller cingulate volumes in the right hemisphere.

The effect sizes of the left/right difference in paracingulate volumes in the midcingulate region were comparable to those for the length analysis reported above (Cohen's d for women = 0.76). To examine how the inclusion of the category overlap affected the results, all analyses were

Table 6 Volumetric analysis using two compartments of the banks of the cingulate and paracingulate sulci in men and women (*M*: male; *F*: female)

Sex	Hemisphere	Cingulate				Paracingulate[a]			
		Postgenual		Pregenual		Postgenual		Pregenual	
		Mean	SD	Mean	SD	Mean	SD	Mean	SD
M	Left	2.89	0.68	2.69	1.13	0.76*	0.67	1.62	1.37
	Right	2.69	0.66	3.10**	1.0	0.56	0.58	1.54	1.52
F	Left	2.67	0.57	2.60	1.04	0.69****	0.60	1.45*	1.45
	Right	2.79	0.67	3.16***	1.09	0.29	0.45	0.94	1.17

Analysis	*df*	*F*	*P*<	*F*	*P*<	*F*	*P*<	*F*	*P*<
	4,395	10.34	0.0001	7.63	0.0001	12.18	0.0001	4.34	0.01
Hemisphere		0.57	NS	19.83	0.0001	31.04	0.0001	4.75	0.05
Sex		3.71	0.055	1.7	0.19	6.48	0.05	8.57	0.01
Interaction		6.12	0.05	0.44	NS	5.83	0.05	1.57	0.21
Gray matter volume		33.5	0.0001	9.35	0.01	0.79	NS	0.0	0.99
Amount of variance explained		9%		7%		11%		4%	

[a] Paracingulate values were log transformed for the statistical analysis to improve the normality of the distributions

Significant effect of hemisphere: * $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$; **** $P < 0.0001$ (post hoc Bonferroni corrected *t* tests of adjusted means)

repeated with that category excluded. The only effect on the analyses was a slight reduction in the strength of the effect of hemisphere on each component.

The volumetric analysis of the paracingulate region that spanned the distance between the AC and the genu (midcingulate region) proved most sensitive to the effect of hemisphere. It was the only analysis that demonstrated a significant asymmetry in men and in this analysis 11% of the variance was explained compared to 8% of the variance explained by the analysis of differences in length.

Question 4 (a) Is there an inverse correlation in the gray matter volumes in the cingulate and paracingulate sulcal banks as suggested by Vogt et al. (1995)? (b) Does this correlation differ in the anterior and midcingulate regions? (c) Is there a sex difference?

The volumes of the cingulate and paracingulate were negatively correlated as was predicted on the basis of Vogt et al. (1995). These correlations were higher for the anterior cingulate (pregenual) (Pearson r (left) $= -0.59$, $P < 0.0001$, (right) $r = -0.53$, $P < 0.0001$) than the midcingulate (postgenual) region (Pearson r (left) $= -0.29$, $P < 0.0001$, (right) $r = -0.25$, $P < 0.001$). For the anterior cingulate (pregenual) region, the correlations did not differ substantially by paracingulate type (Pearson r between $-.039$ and -0.69, $P < 0.01$).

For the anterior cingulate (pregenual) region, the correlations between cingulate and paracingulate volumes were comparable in men and women. In the midcingulate (postgenual) region, however, the correlations on the right side were only significant in women (Pearson r (women) $= -0.51$, $P < 0.0001$, (men) $r = -0.17$, P NS).

Summary

In this large and relatively homogeneous sample of healthy young adults, a series of qualitative and quantitative analyses demonstrated a significant lateral asymmetry in the size of the paracingulate sulcus that, unexpectedly, was much more pronounced in women. The presence of interruptions and unusual orientations rendered the paracingulate and even the cingulate sulcus difficult to identify in many cases. An analysis in which (1) sulcal identity and continuity were ignored, (2) the more dorsal and ventral sulci in regions of overlap were measured as either paracingulate or cingulate, and (3) the measurement was restricted to the midcingulate region between the genu and anterior commissure, proved the most sensitive to the effects of hemisphere.

Discussion

The striking individual variation in the sulcal morphology of the medial frontal cortex has been linked to variation in cytoarchitecture (Vogt et al. 1995; Vogt et al. 2003; Palomero-Gallagher, et al. 2008a; 2008b) and function (Fornito et al. 2004; Crosson et al. 1999). In general, rostroventral areas (anterior cingulate region) are connected with the limbic system and involved in affective regulation while dorsocaudal areas (midcingulate region) are connected with association cortex and the motor system and involved in planning and decision making (Devinsky et al. 1995; Morecraft and Van Hoesen 1998). A cingulofrontal transition area that lies in the banks of the paracingulate sulcus (area 32′) has connections with lateral prefrontal regions and may play a role in generating linguistic responses (Crosson et al. 1999). The relative prominence of this region is increased, on the average, in the left hemisphere but the role that this hemispheric asymmetry plays in functional dominance is unknown due to the rarity with which functional imagers try to localize their activity to defined anatomical morphology (Devlin and Poldrack 2007).

This study arose from our suspicion that investigators attempting to correlate individual differences in cognitive function to individual differences in cingulate morphology might have been daunted by the sulcal complexity of this region and encountered difficulty in analyzing their structural images with the traditional three category system of *prominent*, *present*, and *absent*. We found that not only sulcal category but even sulcal identity was hardly obvious in many cases. In the next sections, we will discuss (1) treatment of intermediate sulcal forms; (2) the effect of anterior boundary (i.e., cingulate region) on asymmetry; (3) how to interpret the asymmetry (and unexpected sex difference); and (4) further implications of sulcal variation.

Intermediate forms

The first question we addressed was how to classify sulcal patterns in which there was only partial overlap between two parallel dorsal and ventral sulci (Fig. 5). Table 3 shows that cases of overlap were more likely to occur in the left hemisphere. If these cases were treated as interrupted cingulate sulci with an *absent* paracingulate, the proportions of cases where the paracingulate was *absent* would no longer demonstrate the expected rightward asymmetry. On the other hand, when a partially overlapping sulcus was treated as a paracingulate, the leftward asymmetry of the *prominent* category increased and became comparable to the proportions in the control samples listed in Table 2. The category pieces, in contrast, had a rightward asymmetry and if shifted into the absent category increased the rightward asymmetry in the category, bringing it more in line with the proportions in the control samples listed in Table 2.

With these considerations in mind the hemispheres were reclassified as described in Fornito et al. (2006a), and the expected leftward asymmetry for *prominent* and rightward asymmetry for *absent* emerged. However, we found the arbitrary nature of the boundary cutoffs for interruptions and gaps, as well as the necessity of making binary decisions on what appeared to be intermediate sulcal forms, disturbing. This anxiety drove the development of a method that did not require sulcal classification or arbitrary length thresholds. This method was more straightforward to teach and use, and because it could be performed rapidly, reliability could be increased with the use of averaged ratings. Interestingly, the results from omitting the classification step and simply counting the number of 1-cm columns with overlapping sulci were similar to those reported in the studies using qualitative categorization.

The fact that application of this method produces a reliable leftward asymmetry obviously begs the question of true validity. Many questions could be asked: what cytoarchitectural regions are found in these interrupted cingulate sulci? Do the axonal connections of the more dorsal of two partially overlapping sulci differ from those of a conventional paracingulate sulcus where there is complete overlap? Do the functional maps that result when activation is registered to individual hemispheres suggest that sulci with partial overlap have less differentiated functions? With functional imagers invested in the anatomical foundations of BOLD signal variation (Devlin and Poldrack 2007) a number of interesting lines of work could be pursued.

Effect of anterior boundary on asymmetry

Functional and structural evidence suggests that anteromedial frontal cortex is divided into a pregenual "emotional" anterior cingulate and a "cognitive" midcingulate region (Vogt et al. 2003; Palomero-Gallagher et al. 2008b). The genu of the corpus callosum coincides roughly with the transition between 24/32 and 24′/32′. In this study, we found that cingulate volumes in the pregenual anterior cingulate region, but not the postgenual, midcingulate demonstrated a significant rightward asymmetry. Rightward asymmetry in the "emotional" anterior cingulate is consistent with the idea that the right hemisphere plays a major role in regulating physiological and behavioral expression of emotion (Blonder et al. 1991; Paus et al. 1996a).

Both pregenual and postgenual paracingulate sulci demonstrated a significant leftward asymmetry but the effect was much more pronounced for the postgenual paracingulate in the "cognitive" midcingulate region. Marked leftward asymmetry in the division that has major connections with prefrontal and motor networks is also consistent with the developing view that left hemisphere networks are critical for action planning and execution (Rushworth et al. 1998; Johnson-Frey et al. 2005).

Sex differences

We have confirmed the existence of a reciprocal relationship between the volumes of the paracingulate and cingulate sulci first suggested by Vogt et al. (1995) (although they used the term superior cingulate sulcus for the sulcus called paracingulate in the present study). We found that the negative correlations between the two sulci were stronger in the pregenual anterior cingulate region than the postgenual midcingulate region due to the fact that men did not show a significant correlation in the midcingulate region. These results suggest that the cingulate and paracingulate sulci may develop in a more independent fashion in the midcingulate than the anterior cingulate region, at least in men. This question clearly deserves further research.

Previous studies of the influence of sex on paracingulate asymmetry have produced varying results. Paus et al. found no evidence for sex hemisphere interactions in two separate studies—a qualitative (Paus et al. 1996b) and a quantitative volumetric one (Paus et al. 1996a). Yucel et al., in contrast, found a marked sex effect for paracingulate frequencies in the left hemisphere. Only 36% of the women had prominent paracingulate sulci, in contrast to 58% of the men (Yucel et al. 2001). Huster et al. (2007) found a complex effect—left handed women and right handed men (but not right handed women and left handed men) had leftward asymmetries in the length of the paracingulate sulcus.

Unexpectedly, our findings did not follow any of the above patterns. In our sample, the women, but not the men, showed a highly significant leftward asymmetry in both qualitative and quantitative assessments, although the significance level for men did finally reach the 0.05 level when the volumetric method was used (Table 6). As the strength of this sex difference did not change when the 26 left handers were eliminated from the sample, the results contrast markedly with those of Huster et al. (2007). The right handed men in the present sample had a marginal asymmetry that only showed up in volumetric measurements while the right handed women had a highly significant asymmetry regardless of method.

It is difficult to make sense of this unpredicted result. It was particularly surprising, given the paucity of sex differences we had found in previous work with this sample (Chiarello et al. 2009a). The women had 17% less cerebral white matter than the men, as expected, but all other sex differences in anatomy virtually disappeared when cerebral volume was entered as a covariate (Leonard et al. 2008). In this study, in contrast, entering gray matter volume had no effect on the paracingulate analyses (Table 6).

In the previous study, the men also showed a trend toward a smaller asymmetry of the planum temporale, due to a larger planum temporale on the right (Chiarello et al. 2009a). It is interesting that the sex difference found in the present study is also in the right hemisphere. It appears that the right and left hemispheres of this sample of men are more similar than would have been expected based either on the literature (Shapleske et al. 1999) or on previous results in our laboratory (Leonard et al. 1993; Leonard et al. 2001; Eckert et al. 2006; Leonard et al. 2006a). The relation between sex and the strength of structural lateralization appears to be affected by as yet unidentified differences in the characteristics of particular samples even when sample size is large.

Strengths and limitations

The protocol under which this sample was recruited and evaluated was designed to test the relation between visual field asymmetries in recognizing and generating words and structural asymmetries in the brain (Chiarello et al. 2004, 2006, 2009a, b). It is a fairly large sample for a structural MRI study. Previous investigations of sex differences in the paracingulate sulcus studied relatively small samples, did not include equal numbers of men and women, lacked evidence that the women and men were comparable on cognitive tests and demography, and used only one measurement technique. On the other hand, the present sample has too few left handers to determine whether the sex difference is modulated by writing hand. In addition, no behavioral tests were included that assessed emotional regulation or complex decision making and thus could be expected to be sensitive to asymmetry of the cingulate sulcus. There are also no functional imaging or diffusion weighted imaging data available that might assist in making structural/functional correlations for various sulcal types.

A major strength of this study was its comparison of three different techniques. Although each technique has strengths and limitations, we feel that the quantitative volumetric technique demonstrates considerable advantages over the qualitative and length estimation techniques. Arbitrary boundaries such as 2 and 4 cm are avoided, gray matter in both the cingulate and paracingulate compartments are included, and the measurement can be made rapidly because the only decision needed is whether there is overlap or not. The fact that measurements made with this technique were most sensitive to the asymmetry provides additional support for its use. Whether, in fact, the measures delineate functionally useful subdivisions will require functional imaging or studies in postmortem material.

Future research

If the measured volume of the pregenual paracingulate sulcus gave some indication of the size of the cytoarchitecturally defined area 32′ in the midcingulate region, the present findings would imply that this region is more asymmetric than area 32 in the anterior cingulate region. Unfortunately, the relationship between the extent of nonprimary cytoarchitectonic areas and sulcal volumes can be quite variable (Amunts et al. 2003; Fischl et al. 2008). Diffusion imaging experiments tracing fiber connections from identified sulci and more functional imaging experiments like those of Crosson et al. (1999) and Fink et al. (1997) will be necessary to determine the functional correlates of these asymmetries.

It is well known that profound inter individual differences are found in the sulcal patterns of the human brain. These differences provide important information about genetic and developmental history (Lohmann et al. 1999; Eckert et al. 2002; White et al. 2002; Rivera et al. 2005; Leonard et al. 2006b) and fiber connections (Van Essen 1997). The development of cortical convolutions has been successfully simulated in 2D by varying plasticity, elasticity and growth rate (Toro and Burnod 2005). These authors raise the possibility that early morphogenetic folding may introduce “large-scale geometric anisotropies for the diffusion of [molecular] signals” (p. 1910). In animals, perturbation of such molecular signals early in development can produce the duplication of functionally and cytoarchitecturally defined regions (Fukuchi-Shimogori and Grove 2001; Grove and Fukuchi-Shimogori 2003). Toro and Burnod suggest that the physical barriers posed by convolutions might actually influence the regional distribution of distinct cortical zones. It is tempting to speculate that the development of formations where sulci can not be unambiguously identified (Figs 1c, 6) are the result of perturbations in the early cortical environment (Goldman and Galkin 1978; Hilgetag and Barbas 2006).

Such speculations could be tested in an animal model with cortical convolutions—such as the ferret (Smart and McSherry 1986) or the dog, where the recent sequencing of the genome raises the possibility of experiments on the association between genetic polymorphisms in transcription factors or other molecular signals and the interactive development of cortical folding, cytoarchitecture, and fiber connections (Parker et al. 2004; Karlsson and Lindblad-Toh 2008; Sutter et al. 2008; Chen et al. 2009).

The paracingulate sulcus appeared relatively recently in primate evolution and is not found on the medial wall of macaques or apes (Leonard et al. 2006b). Variable sulcal patterns may constitute little experiments in evolution with different sulcal patterns selected for particular ecological niches. Although a paracingulate sulcus is clearly not required for successful negotiation of modern life, there is some, admittedly scant, evidence that the cortical distribution of functions in individuals with and without a paracingulate sulcus is different (Crosson et al. 1999; Fornito et al. 2004; Fornito et al. 2006b).

The task of decoding the functional implications of different sulcal patterns is challenging because the regional differences in cortical architecture they imply are only one factor affecting behavioral performance, personality, and diagnosis (Cannon et al. 1999). Individual experiences in the womb, the family, and school combine to modulate the behavioral effects of the genetic and developmental forces on the brain (Eckert et al. 2001; Isaacs et al. 2008). An understanding of the relationship between cortical patterns and behavior may require attention to the influence of a host of moderating variables.

One neglected area of research is the relationship between term birth, birth weight, and sulcal pattern. The cortical sulci develop during the last trimester of fetal life (Dubois et al. 2008). Are there differences in the sulcal patterns of individuals who develop in an incubator, rather than the womb? One could predict a closer relationship between genetic markers, family membership and sulcal pattern in big babies born at term than in those with less privileged developmental histories (Eckert et al. 2002).

The sulcal architecture of the medial wall is complex. The geometric arrangement and asymmetry of different functional zones varies dramatically between individuals. There are now many tools available to characterize this variability in MRI scans (Mangin et al. 2004; Van Essen and Dierker 2007; Fischl et al. 2008). It is difficult to fathom how an imaging program that ignores this sulcal complexity can hope to decode the functional architecture of this interesting region. Perhaps the day will come when individual differences in cortical morphology will be seen as a tool rather than as a barrier to understanding (Scheperjans et al. 2008).

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