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Size Matters: Cerebral Volume Influences Sex Differences in Neuroanatomy

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Biological and behavioral differences between the sexes range from obvious to subtle or nonexistent. Neuroanatomical differences are particularly controversial, perhaps due to the implication that they might account for behavioral differences. In this sample of 200 men and women, large effect sizes (Cohen's $d > 0.8$) were found for sex differences in total cerebral gray and white matter, cerebellum, and gray matter proportion (women had a higher proportion of gray matter). The only one of these sex differences that survived adjustment for the effect of cerebral volume was gray matter proportion. Individual differences in cerebral volume accounted for 21% of the difference in gray matter proportion, while sex accounted for an additional 4%. The relative size of the corpus callosum was 5% larger in women, but this difference was completely explained by a negative relationship between relative callosal size and cerebral volume. In agreement with Jancke et al., individuals with higher cerebral volume tended to have smaller corpora callosa. There were few sex differences in the size of structures in Broca's and Wernicke's area. We conclude that individual differences in brain volume, in both men and women, account for apparent sex differences in relative size.

Keywords: asymmetry, corpus callosum, gray matter, human, planum temporale

Introduction

Biological and behavioral differences between the sexes range from obvious to subtle or nonexistent. Among the most controversial have been neuroanatomical differences because of the implication that behavioral differences could be due to fundamental differences in brain organization or neural potential (Halpern et al. 2007). The current study, part of the Biological Substrates for Language Project, affords the opportunity to explore this issue in 200 college-aged men and women. Reported sex differences in neuroanatomy include highly reliable differences in cerebral volume (Willerman et al. 1991; Andreasen et al. 1993), cerebellar volume (Filipek et al. 1994), and gray matter proportion (Gur et al. 1999; Allen et al. 2003) and less reliable differences in the asymmetries (reviewed by Beaton 1997; Shapleske et al. 1999) and proportional sizes of various language areas (Harasty et al. 1997; Rademacher et al. 2001; Knaus et al. 2006; Vadlamudi et al. 2006). The reports of sex differences in shape and proportional size of the corpus callosum are relatively more consistent (Witelson 1989; Allen et al. 1991; Steinmetz et al. 1992; Driesen and Raz 1995; Bishop and Wahlsten 1997; Davatzikos and Resnick 1998; Luders et al. 2003).

We were particularly intrigued by the possibility that certain structures occupy proportionally more brain volume in women than men. This is a significant claim given the strong relation

that normally exists between subregion size and total volume. After an exhaustive study of 131 species of mammals, Finlay and Darlington concluded that "the most likely brain alteration resulting from selection for any behavioral ability may be coordinated enlargements of the entire nonolfactory brain" (Finlay and Darlington 1995, p. 1578). A demonstration that selected structures were proportionally increased in women would suggest that sex differences in behavior had been accompanied by a biologically unusual targeted enlargement of specific regions or networks. Most notably, these claims have been made for gray matter volume, corpus callosum, and perisylvian language regions.

- 1) In a study of 80 men and women, Gur et al. (1999) found that the slope of the relation between gray matter and cerebral volume differed in men and women. Women but not men with higher cerebral volume had proportionally more gray matter. This sex difference was not found in a more recent study of 100 men and women (Luders et al. 2002).
- 2) Two post mortem studies (with n 's of 21 and 27, respectively) have found proportionally larger perisylvian regions in women. Harasty et al. (1997) found that the planum temporale and inferior frontal gyrus were 30% and 20% larger relative to cortical volume. Rademacher et al. (2001) found that the primary auditory cortex on Heschl's gyrus was relatively larger in females, particularly in the right hemisphere. Two magnetic resonance imaging (MRI) studies (with n 's of 48 and 42, respectively), however, failed to replicate these sex differences in proportional size or asymmetry (Knaus et al. 2006; Vadlamudi et al. 2006).
- 3) In a study of 121 men and women Jancke and his associates found that the robust sex difference in proportional size of the corpus callosum (Driesen and Raz 1995; Bishop and Wahlsten 1997) was explained by sex differences in brain volume. That is, small brains had proportionally larger callosa than large brains (Jancke et al. 1997).

All the above reports acknowledge a large and reliable sex difference in cerebral volume. The question is whether selection has favored a sex-dependent redistribution of tissue volumes, perhaps as an adaptation to some constraint on brain size in women (Hrdy 1999).

In this study we contrasted this hypothesis with the hypothesis that individual differences in brain volume, in both men and women, account for what appear to be sex differences in the proportion of various tissue components. We compared the raw volume means for tissue volumes, corpus callosum area, and the surface areas of 5 perisylvian regions: the planum temporale, planum parietale, Heschl's gyrus, pars triangularis

and pars opercularis (see illustrations in Fig. 1). We then performed hierarchical regression and analyses of covariance to examine the unique contribution of sex to differences in size after accounting for the effect of cerebral volume.

Method

Subjects

Brain imaging and selected demographic data were collected on 100 men and 100 women recruited from a university community. 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 MRI scan. The men and women did not differ in mean age (21.7 vs. 21.5 years), parental education (3.40 vs. 3.25 with 5 representing a professional degree), hand preference (+0.67 vs. +0.74; 1 = completely right handed) (Bryden 1982), Passage Comprehension (67.0% vs. 63.0%) (Woodcock 1998), or short form estimates of Verbal (108.7 vs. 108.8) and Performance (110.3 vs. 107.3) 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 scored less than 0.3 on the Bryden (1982) scale of hand preference (this group included all the individuals who wrote with their left hand and 2 additional individuals, one man and one woman, who wrote with the right hand). All of the analyses reported here were conducted with and without the non right handers. As the inclusion of non right handers did not alter any of the results, we report findings for the entire sample.

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. Preprocessing the images was performed using 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 web site. Volumes, surface areas, means, and standard deviations were automatically accumulated in a data file for statistical analysis. Each structure was measured twice by at least 2 different investigators who were blind to hemisphere and subject characteristics. When there was more than 15% disagreement between the average values for the 2 measurements, the experimenters conferred and identified the reason for disagreement and then remeasured until the 2 measures agreed.

Measurements

Gray, white, and CSF volumes of each cerebral hemisphere were estimated by outlining every fifth sagittal image starting at the midline. The brainstem was excluded by transection in the midcollicular plane. The midsection was traced twice and half the slab volume added to each hemisphere. This interrater reliability of this measure is >0.98 (intra class correlation). Preliminary studies showed that the accuracy of volumes sampled in this way was equivalent to that in which every section was measured. The volume of the frontal lobe was estimated by using the central sulcus as a boundary. The volume of the parietal operculum was estimated by tracing the area enclosed by Heschl's sulcus, the posterior ramus of the Sylvian fissure and the postcentral sulcus. The interrater reliability of these measures is >0.90 (intra class correlation). The total volume of each cerebellar hemisphere was estimated by outlining every sixth sagittal image starting at the midline. The midsection was traced twice and half the slab volume added to each hemisphere (automated segmentation of the cerebellum was not acceptable on these images). The interrater reliability of this measure is >0.95 (intra class correlation). The area of the corpus callosum was extracted from the midsagittal white matter image. It was subdivided into 7 subdivisions (rostrum, genu, anterior, mid and posterior body, isthmus, and splenium) using the method of Witelson (1989).

Surface areas of the planum temporale and planum parietale were calculated between Talairach coordinates (mm), $x = 47-56$ (standard sagittal positions normalized for hemisphere width and chosen to maximize lateral asymmetry as well as reliability; Leonard et al. 1996; Eckert et al. 2001; Chiarello et al. 2004). In individuals with one clearly defined Heschl's gyrus, the anterior border of the planum temporale was defined as the depth of the sulcus that formed the posterior border of Heschl's gyrus (Heschl's sulcus). The posterior boundary was defined as the origin of the posterior ascending ramus or the termination of the Sylvian fissure. At medial positions, the origin of the parietal bank is absent or difficult to distinguish, whereas in more lateral positions the anterior border of the planum frequently becomes indistinct. Interrater

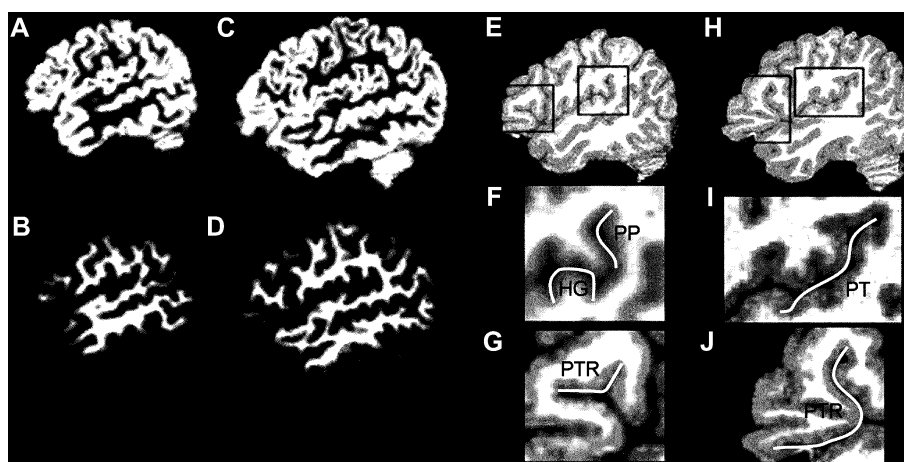


Figure 1. Sagittal images. (A) Partial volume estimate (PVE) image of gray matter in individual with low cerebral volume. The percentage of gray matter in each pixel is estimated on a scale ranging from 0 (black) to 1 (white). (B) PVE image of white matter in individual A. (C) PVE image of gray matter in individual with high cerebral volume. (D) PVE image of white matter in individual C. (E) T1 weighted image of left hemisphere with small pars triangularis (PTR), Heschl's gyrus (HG), planum temporale (PT), and relatively large planum parietale (PP). Boxes depict regions magnified in (F and G). (H) T1-weighted image of left hemisphere with large PTR, HG, PT, and absent PP. Boxes depict regions magnified in (I and J). White lines in (F), (G), (I), and (J) are tracings of surface areas.

reliability for these measurements was 0.85. A comparative study of techniques to measure the planum temporale (Best and Demb 1999) found that asymmetry measures using this index agreed well with those gained using other techniques. The surface area of the primary Heschl's gyrus was measured between Talairach $x = 34$ – 48 . Interrater reliability was 0.9 for H1. The pars triangularis in the inferior frontal gyrus (part of Broca's area on the left) was measured from Talairach $x = 39$ – 48 by tracing the surface formed by the anterior ascending ramus (AAR) and the anterior horizontal ramus (AHR) of the Sylvian fissure. The surface was traced from the dorsal tip of the AAR, ventrally to the Sylvian fissure and then following the AHR to its termination (Foundas et al. 1998). Interrater reliability for this measurement was 0.85. The pars opercularis in the inferior frontal gyrus (part of Broca's area on the left) was measured from Talairach $x = 35$ – 44 . The surface was measured by tracing the convolutions on sagittal sections, starting at the AAR of the Sylvian fissure and ending at the anterior subcentral sulcus. This method was developed by (Foundas et al. 1998). Interrater reliability for this measurements was 0.85.

Statistical Analysis

All variables were entered into spreadsheets and analyzed with PC-SAS (SAS 2007). Student's t -tests were used to assess cognitive, demographic, and anatomical differences between the sexes. Statistical significance thresholds were not corrected for multiple comparisons because we decided to follow the APA Task Force on Statistical Testing recommendation to focus on effect sizes (estimated with Cohen's d ; Cohen 1977). The degree of association between variables was tested with correlation analysis (Pearson r). Because the goals of the study were 1) to determine whether women have proportionally larger structures than men; and 2) the extent to which sex differences in these proportions are accounted for by sex differences in cerebral volume, we created new variables (proportional or relative sizes) by dividing selected tissue volumes and surface areas by cerebral volume (summed CSF, gray matter, and white matter). Student's t -tests were conducted to determine if there were sex differences in these new variables and then the relation between these new variables and cerebral volume was examined graphically and with correlation methods to determine if larger proportional volumes were associated with smaller cerebral volume, regardless of sex. Hierarchical multiple regression was used to determine the relative significant of cerebral volume (step 1) and sex (step 2) to these proportions. The interaction between cerebral volume and sex was entered in step 3. We

also performed analysis of covariance (ANCOVA) as a more direct method of comparing the relative magnitudes of the contributions of sex and cerebral volume to brain structure size.

The term proportion is used somewhat loosely in the preceding paragraph. Gray and white matter proportions are true proportional volumes or ratios because the units of measure are the same as that of cerebral volume. In the case of the corpus callosum and perisylvian structures, however, the units in numerator and denominator are not the same and it is inaccurate to refer to the quotient as a ratio or a proportion. We therefore refer to these quotients as relative sizes (O'Brien et al. 2006). Smith has discussed the difference between controlling for the effect of a variable and creating a proportion or relative value (Smith 2005). The distinction becomes important because it is sometimes argued that it is improper to control for the influence of a variable if this variable only covaries with the variable of interest in one group. In such a case it appears that the effect of cerebral volume is actually introduced into one group while controlled for in the other group. When creating a proportion or relative value, there is no requirement that the denominator correlate with the numerator, according to Smith (2005).

Results

Cerebral Volumes and Surface Areas

The means and standard deviations for cerebral volumes and surface areas in the 2 sexes are presented in Tables 1 and 2. Men had a 13% larger cerebral volume (17% more white matter and CSF, 10% more gray matter) and a 10% larger cerebellum. The effect sizes for these differences ranged from 0.8 to 1.5. There was a somewhat smaller effect of sex in the size of the corpus callosum (effect size of 0.59), and the size of this difference did not vary substantially across callosal region. Women had a marginally smaller planum temporale in the right hemisphere (effect size of -0.29). There were no sex differences in the surface areas of any of the other measured perisylvian regions.

Histograms of the distributions of cerebral volume and left planum temporale surface area in the 2 sexes are shown in

Table 1

Means and standard deviations for brain measures in 100 men and 100 women (F: female; M: male), and test of sex differences for each structure.

Measure	Sex	Left					Right																																																																																																																																																						
		Mean	SD	t	P	Effect	Mean	SD	t	P	Effect																																																																																																																																																		
CSF	F	75	13	-6.96	<0.0001	-0.99	83	14	-7.13	<0.0001	-1.01																																																																																																																																																		
	M	88	14				98	14				Gray	F	288	26	-7.83	<0.0001	-1.13	291	26	-7.39	<0.0001	-1.05	M	318	28	319	27	White	F	216	26	-10.24	<0.0001	-1.45	219	26	-10.75	<0.0001	-1.50	M	255	27	260	28	Hemisphere	F	579	55	-10.29	<0.0001	-1.44	593	56	-10.40	<0.0001	-1.49	M	661	59	677	57	Cerebellar hemisphere	F	71	9	-5.49	<0.0001	-0.84	71	9	-5.39	<0.0001	-0.78	M	79	10	78	9	Planum temporale	F	3.19	0.81	-0.79	0.43	-0.11	2.27	0.92	-2.08	0.04	-0.29	M	3.29	0.97	2.55	0.97	Planum parietale	F	1.12	0.74	-0.74	0.46	-0.11	1.73	0.87	-0.60	0.55	-0.09	M	1.20	0.81	1.81	0.95	Heschl's gyrus	F	3.27	0.61	-0.16	0.87	-0.02	2.86	0.46	-0.19	0.85	-0.03	M	3.29	0.53	2.88	0.44	Pars triangularis	F	3.10	0.76	-0.88	0.38	-0.13	2.90	0.84	-0.79	0.43	-0.11	M	3.21	0.90	3.00	0.91	Pars opercularis	F	4.31	0.52	-0.83	0.41	-0.12	4.07	0.52	-1.05
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Table 2

Means and standard deviations for subcomponents of corpus callosum in 100 men and 100 women measured according to Witelson (1989) and test of sex difference for each structure.

Measure	Sex	Mean	SD	<i>t</i>	<i>P</i>	Effect
Total	F	5.42	0.81	-4.18	<0.0001	-0.59
	M	5.94	0.92			
Genu	F	1.15	0.22	-3.49	0.001	-0.50
	M	1.27	0.26			
Splenius	F	1.57	0.26	-2.74	0.007	-0.39
	M	1.68	0.27			
Isthmus	F	0.49	0.13	-3.01	0.003	-0.43
	M	0.54	0.14			
Antbody	F	0.75	0.16	-4.11	<0.0001	-0.58
	M	0.84	0.16			
Midbody	F	0.69	0.12	-3.98	<0.0001	-0.56
	M	0.76	0.13			
Postbody	F	0.65	0.12	-3.32	0.001	-0.47
	M	0.71	0.14			

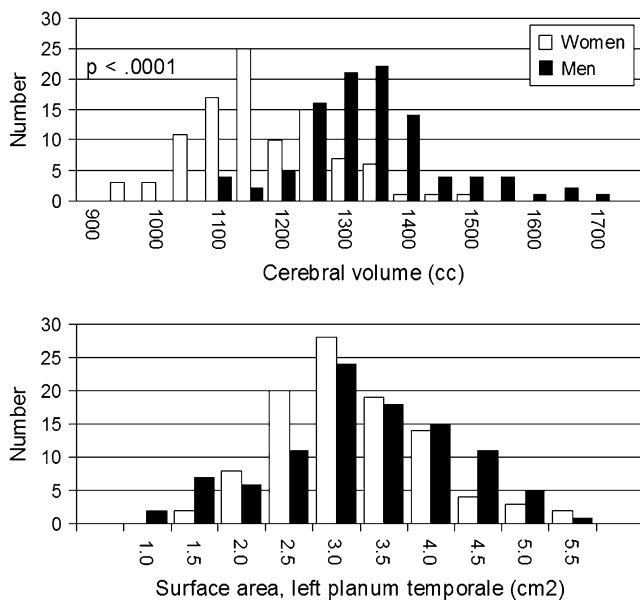


Figure 2. Histograms of the distribution of cerebral volume (top) and left hemisphere planum temporale surface area (bottom) in 100 men and 100 women. Note the large range of individual differences in each measure. Although there is a relatively small degree of overlap in cerebral volume, the distributions of left planum temporale surface area overlap completely.

Figure 2. Although there is relatively little overlap in the distributions of cerebral volume and a large overlap in the distributions of left planum temporale size, the range of variation for both measures is wide and equivalent in both men and women.

Influence of Cerebral Volume

Figure 3 shows scatter plots of the relation between cerebral volume and the size of the cerebellum, corpus callosum, and the raw volumes of gray matter, white matter and CSF. There is very little difference between the shape of the relationships in men and women. There are 2 outliers on the corpus callosum graph. Two men had very large corpus callosa. Even after

careful inspection of the images for artifacts and repeated remeasuring by different operators, these points remained as outliers. Their removal did not change the shape of the regression line, however. As indicated in Figure 3, the slopes of gray and white matter against cerebral volume are roughly parallel in both men and women.

Table 3 lists the correlation coefficients (Pearson *r*) between cerebral volume and the 1) raw size and 2) relative size of selected measures. For gray matter, the cerebellum and the corpus callosum, there is a consistent relation between the 2 relationships in both men and women. If the raw size of a brain structure is *positively* correlated with cerebral volume, its proportional or relative size is *negatively* correlated, that is, proportions and relative sizes are larger in individuals with lower cerebral volume, regardless of sex. For the perisylvian structures, the relations are more inconsistent although the same general trend is apparent.

Table 4 gives the means and standard deviations for the relative size of selected brain structures in men and women. Women had a 2% larger proportion of gray matter (effect size of 0.98) and a 1% smaller proportion of white matter than men (effect size of 0.78). The relative size of Heschl's gyrus was 11% larger on the left (effect size of 0.67) and 15% larger on the right (effect size of 0.75) for women. The relative sizes of the left planum temporale, cerebellum, and corpus callosum were also larger in women but the effect sizes of these differences were more modest, ranging from 0.29 to 0.33. Although the right planum parietale, both parietal opercula and frontal lobes showed a significant dependence on cerebral volume, there were no sex differences in the proportions (data not shown).

Sex differences in the relationships between relative structure size and cerebral volume were modest (except for the planum temporale) and were explored graphically (Fig. 4) and with hierarchical multiple regression (Tables 5 and 6). Figure 4 shows that women have higher proportional volumes of gray matter, especially for lower values of cerebral volume. The 2 regression lines converge very slightly for large cerebral volumes. Hierarchical multiple regression analysis was performed entering cerebral volume in step 1 and sex in step 2. This analysis showed that cerebral volume accounted for 21% of the variance in proportional gray matter volume, while sex accounted for an additional 4%. Sex also contributed a modest 1% of the variance in white matter proportion and 2% and 3% of the variance in the relative size of the left and right Heschl's gyri (Table 6). The contribution of sex to variance in cerebellar proportion and relative corpus callosum size and was not significant (Table 5).

Parallel analyses using ANCOVA were performed to determine the contribution of sex to brain structure size after controlling for cerebral volume. Table 7 demonstrates that the results of this analysis were quite similar to the results of the regression analysis. The effects of sex on brain structure size are modest compared with the effects of cerebral volume, regardless of statistical procedure. Even in the case of the left planum temporale, the results are roughly comparable. Both methods show that there is an interaction between sex and cerebral volume in that planum size correlates with cerebral size only in men. Left planum temporale size is elevated in women, but not men, with small cerebral volume. Cerebral volume is a significantly stronger predictor of left planum temporale size in males compared with females ($z = 1.65$, $P < 0.05$; Cohen and Cohen 1983).

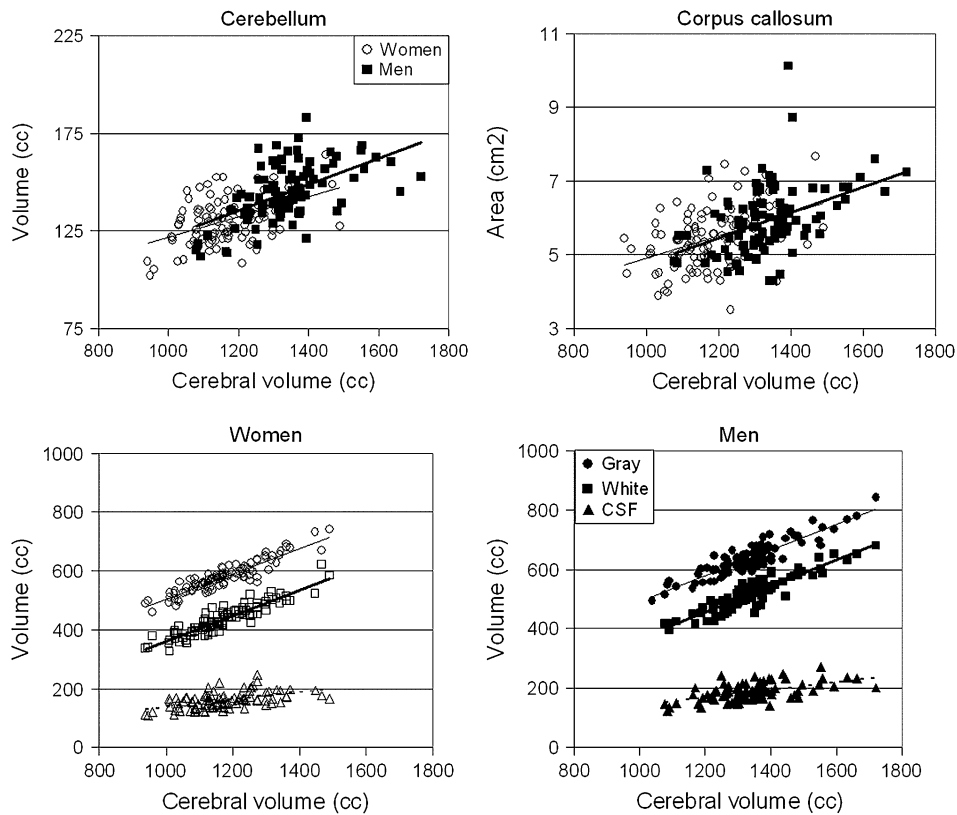


Figure 3. Top: Cerebellar volume and corpus callosum area have similar relationships with cerebral volume in men and women. Bottom: The slopes of gray matter, white matter and CSF against cerebral volume are similar in women (left) and men (right). Correlation coefficients are given in Table 3.

Table 3
Correlation coefficients (Pearson *r*) describing the relationship between cerebral volume and the raw and relative size of selected brain structures in men and women.

Brain measure	Raw size		Relative size	
	F	M	F	M
Gray matter	0.92****	0.90****	-0.32**	-0.23*
White matter	0.92****	0.92****	0.32**	0.27**
CSF	0.54****	0.55****	-0.01	-0.02
Cerebellum	0.27**	0.34***	-0.42****	-0.33***
Corpus callosum	0.42****	0.44****	-0.23*	-0.13
Left planum temporale	0.05	0.27**	-0.31**	0.01
Right planum temporale	0.02	0.25*	-0.23*	0.02
Right planum parietale	0.31***	0.09	0.11	-0.07
Left Heschl's gyrus	0.41****	0.24*	-0.13	-0.27**
Right Heschl's gyrus	0.37***	0.20*	-0.23*	-0.32**

Note: **P* < 0.05; ***P* < 0.01; ****P* < 0.001; *****P* < 0.0001.

Discussion

The goal of this study was to determine whether previous reports of sex differences in gray matter, corpus callosum, and perisylvian area size could be verified in a large normative sample of young adults. We found that men had 17% more cerebral white matter, 10% more gray matter and a 10% larger corpus callosum. In general, individuals with larger cerebral volumes tended to have relatively less gray matter, and relatively smaller corpora callosa and perisylvian areas. Hierarchical multiple regression analysis determined that most of the variation in these relative values was due to individual differ-

Table 4
Means and standard deviations of relative or proportional size of selected brain structures.

Relative size	Sex	Mean	SD	<i>t</i>	<i>P</i> <	Effect
Gray matter	F	0.494	0.018	6.89	<0.0001	0.98
	M	0.476	0.018			
White matter	F	0.371	0.019	-5.52	<0.0001	-0.78
	M	0.385	0.017			
CSF	F	0.139	0.019	-1.57	0.12	-0.2
	M	0.142	0.017			
Cerebellum	F	0.122	0.016	2.05	0.042	0.3
	M	0.117	0.014			
Left planum temporale	F	0.0027	0.0007	2.80	0.001	0.29
	M	0.0025	0.0007			
Right planum temporale	F	0.002	0.0007	0.48	0.63	0.13
	M	0.0019	0.0008			
Left Heschl's gyrus	F	0.0028	0.0005	5.34	0.0001	0.67
	M	0.0025	0.0004			
Right Heschl's gyrus	F	0.0025	0.0004	5.77	0.0001	0.75
	M	0.0022	0.0004			
Corpus callosum	F	0.0046	0.0006	2.21	0.028	0.33
	M	0.0044	0.0006			

ences in cerebral volume and only 1% to 5% of the variation was uniquely accounted for by sex. These results were confirmed with ANCOVA in which cerebral volume was controlled rather than used to create a proportional measure.

It is now possible to answer the 3 questions posed in the introduction.

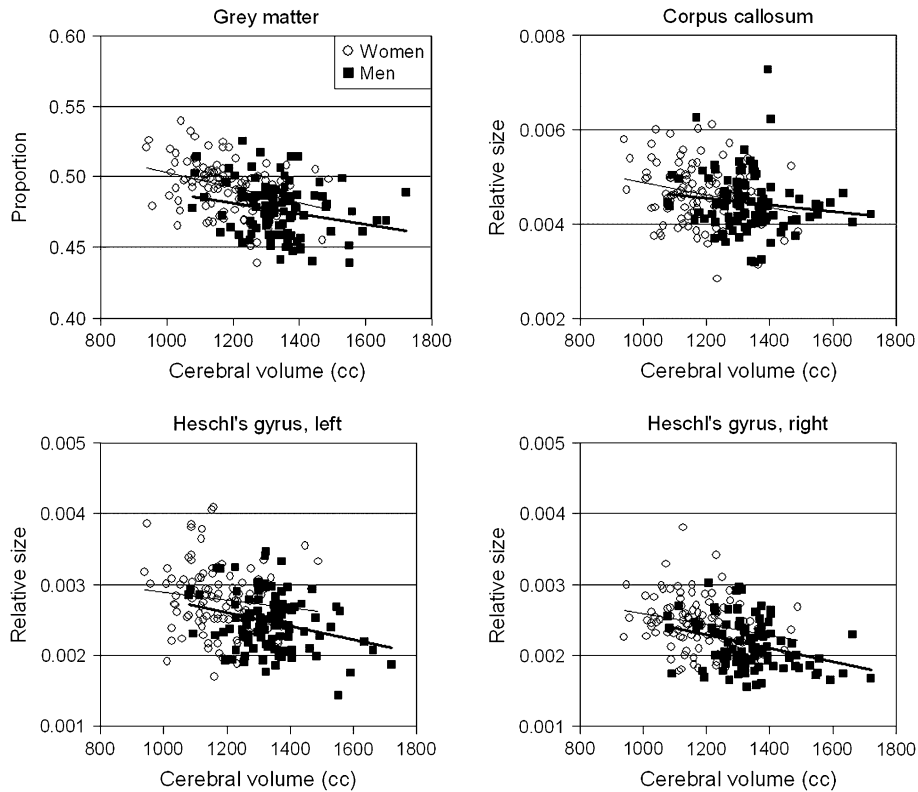


Figure 4. Gray matter proportion and the relative size of the corpus callosum and Heschl's gyrus plotted as a function of cerebral volume. All measures show a negative relation with cerebral volume (see Tables 3, 5, and 6).

Table 5

Hierarchical multiple regression analysis of the contribution of cerebral volume (CV) (entered in step 1) and sex (step 2) to proportional or relative size of brain structures.

Relative size	Level		R^2	ΔR^2	$P <$	Std. beta	t	$P <$
Gray matter	1	CV	0.21		0.0001	-0.46	-7.28	0.0001
	2	CV		0.04	0.0001	0.31	-3.99	0.0001
		Sex				0.26	-3.36	0.001
White matter	1	CV	0.19		0.0001	0.43	6.87	0.0001
	2	CV		0.01	0.0001	0.34	4.35	0.0001
		Sex				0.16	2.05	0.05
Corpus callosum	1	CV	0.05		0.001	-0.23	-3.39	0.001
	2	CV		0.00	0.005	-0.22	-2.55	0.05
		Sex				-0.02	-0.29	0.78
Cerebellum	1	CV	0.14		0.0001	-0.38	-5.86	0.0001
	2	CV		0.01	0.0001	-0.46	-5.69	0.0001
		Sex				0.13	1.62	0.11

Note: The interaction between cerebral volume and sex did not contribute significant additional variance (data not shown).

1) Do women show an increased proportion of gray matter as cerebral volume increases as Gur et al. (1999) found?

Our data suggest that the opposite relationship holds, and that, as Luders et al. (2002) originally reported, both women and men with lower cerebral volumes have higher proportions of gray matter with the relationship slightly stronger in women (Tables 3 and 4 and Fig. 4).

2) Is the difference in relative size of the corpus callosum in women completely accounted for by differences in cerebral volume as Jancke et al. (1997) proposed? Our data support Jancke et al. (1997). Sex did not contribute unique variance

Table 6

Hierarchical multiple regression analysis of the contribution of cerebral volume (CV, entered in step 1) and sex (entered in step 2) to the relative size of perisylvian areas. The interaction between sex and cerebral volume (entered in step 3) contributed additional significant variance to the relative size of the left planum temporale, only.

Relative size	Level		R^2	ΔR^2	$P <$	Std. beta	t	$P <$	
Left planum temporale	1	CV	0.05		0.001	-0.24	-3.47	0.001	
	2	CV			0.00	0.00	-0.19	-2.22	0.05
		Sex					-0.08	-0.95	0.34
	3	CV		0.02	0.001	-1.14	-2.61	0.01	
		Sex					-1.78	-2.31	0.05
		Interaction					2.39	2.22	0.05
Left Heschl's gyrus	1	CV	0.12		0.0001	-0.36	-5.36	0.0001	
	2	CV		0.03	0.0001	-0.22	-2.76	0.01	
Right Heschl's gyrus		Sex					-0.22	-2.72	0.01
	1	CV	0.18		0.0001	-0.43	-6.68	0.0001	
	2	CV		0.02	0.0001	-0.31	-3.98	0.0001	
	Sex					-0.19	-2.44	0.05	

to the relationship between relative corpus callosum size and cerebral volume, as indicated in Table 5. Both women and men with lower cerebral volumes have relatively larger callosa.

3) Do women have proportionately larger structures in perisylvian regions related to language as Harasty et al. (1997) and Knaus et al. (2004) have reported?

Our data largely agree with these previous reports. Women had relatively more surface area in the left planum temporale and left and right Heschl's gyri (Table 4). But once again, this

Table 7

Comparison of results using 2 methods for comparing the effects of cerebral volume and sex to variation in brain structure size: ANCOVA (first 3 columns) and the creation of a proportion or relative size by dividing by cerebral volume (column 4).

	F			Contribution of sex to variation in relative size
	Model	Cerebral volume	Sex	
Corpus callosum	32.7***	44.0***	0.81	No
Left planum temporale	3.25*	5.85*	0.63	Interaction
Right planum temporale	3.65*	2.95~	0.43	No
Left Heschl's gyrus	11.7***	23.3***	7.47**	Yes
Right Heschl's gyrus	8.60***	17.2***	5.31*	Yes
Cerebellum	27.3***	20.9***	3.79	No

Note: The results of the analyses of relative size are presented in Tables 5 and 6. ~ $P < 0.10$, * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$.

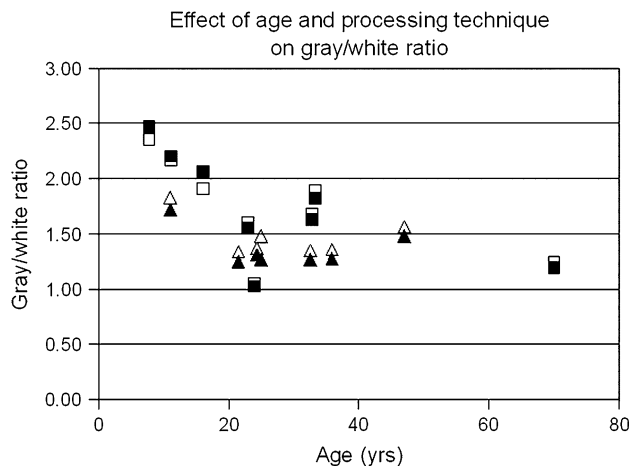


Figure 5. Effect of age and image processing method on the ratio between gray and white matter. Data and references are given in Table 8. Although the gray/white ratio declines with age and is generally higher in women, gray white ratios appear to be more consistent in images that have not been normalized (rescaled) to a template. Open symbols: women; solid symbols: men; Squares: images normalized and modulated (values adjusted for cerebral volume); Triangles: images segmented and measured in native (actual) space, although aligned to standard axes.

apparent sex difference was usually due to sex differences in cerebral volume. Except in the case of the planum temporale in the left hemisphere, individuals with smaller brains, regardless of sex, had relatively larger structures (Fig. 4).

The major findings of the present study are that women and men have very reliable differences in cerebral volume that account for much of the variance in brain structure size that at first glance might appear to be attributable to sex. In the discussion below we will attempt to integrate these findings into the previous literature and discuss how methodological choices might affect the findings.

There have been multiple reports of sex differences in cerebral volume. Table 8 compares our results to that of 13 published studies using a variety of image processing methods. Substantial size differences are found regardless of method. In young adults the sex differences in gray matter volume range from 6% to 12% and the sex differences in white matter volume range from 9% to 23%. The differences found in this study sit squarely in the middle of these ranges at 10% and 17%. Given that the effect size of the sex difference in raw gray matter volume is greater than 1, the data do not support the statement

that women and men have “similar absolute volumes of gray matter” (Halpern et al. 2007, p. 25).

The sex difference in cerebral volume is frequently attributed to sex differences in physical size. Across ethnic groups there is a very strong relationship between body size and cerebral volume when the means of cranial capacity and body size are plotted against each other (Peters et al. 1998). This relationship disappears when examined within any one sample. In a recent report on 100 post mortem analyses, Witelson et al. (2006) found that only 1–4% of the variance in brain weight could be attributed to differences in height. Other reports have found a significant correlation between height and volume in men but not women (Koh et al. 2005; Heymsfield et al. 2007) or women but not men (Peters et al. 1998; Nopoulos et al. 2000). Given these inconsistencies, it does not appear that adjusting cerebral volumes for physical characteristics such as height or weight is necessary or useful (Striedter 2005).

Proportional Differences in Gray Matter

Perhaps to minimize the significance of sex differences in absolute cerebral size, studies have focused on the fact that women appear to have relatively more gray matter per cubic centimeter than men. This difference was small but robust. Although the proportional volume of gray matter was only 2% larger in women than in men, the effect size of this difference was 0.98 (see Table 4). Most of this sex difference, however, was explained by individual differences in cerebral volume—smaller brains tended to have larger proportions of gray matter (see Fig. 4), although sex did contribute a unique additional 4% of the variance (see Table 5). This sex difference in gray matter proportion (frequently expressed as a gray/white ratio) has been found in many previous studies (see Table 8 and Fig. 5). Despite a clear effect of age (gray white ratios are high in childhood and rise again at the end of life; Allen et al. 2005) and processing technique (images that are normalized i.e., nonlinearly scaled to a template, tend to have higher ratios), women still have higher gray to white matter ratios in every study except one in children and adolescents (Wilke et al. 2007).

Two previous studies appear to have looked at the effect of cerebral volume on this ratio. Gur et al. (1999) found that the amount of gray matter increased more rapidly with cerebral volume in women than men, whereas Luders et al. (2002) reported no sex difference in the relationship. Our results, in a much larger sample, agree with those of Luders. The relative proportion of gray matter decreased with cerebral volume and the slopes were comparable in men and women (see Fig. 4). The fact that there is such a consistent relation between gray matter proportion and cerebral volume suggests that the optimal relation between neurons, glia, and axons may depend more on surface area (Seldon 2005) and speed of transmission (Ringo et al. 1994) than on sex hormones or chromosomal sex. Theoretical analyses suggest that the ratio of gray to white matter conforms to that which would be predicted if neurons in large and small brains kept the same number of connections rather than scaling up the number of connections as the number of neurons increased (Striedter 2005). White matter increases disproportionately faster than gray matter and the ratio over a wide range of mammals from shrews to humans is closely predicted by a power law with an exponent of 4/3. The shape and gray/white configuration of the cerebral cortex is that expected if fiber connections obey a requirement of

Table 8

Effect of image processing method and age on tissue volumes and ratio.

Study	Sex	N	Age (years)	Volume (cc)		Ratio (G/W)	% Difference	
				Gray	White		Gray	White
Brain images registered to a template with results statistically adjusted for differences in cerebral volume								
(Wilke et al. 2007)	F	34	8	789	336	2.35		
		34	11	758	350	2.17		
	M	34	16	686	359	1.91		
		33	7	891	361	2.47	-12.1%	-7.2%
		32	11	837	380	2.20	-9.9%	-8.2%
		33	15	808	392	2.06	-16.3%	-8.8%
(Nopoulos et al. 2000)	F	42	23	697	436	1.60	-8.9%	-11.7%
	M	42	23	762	490	1.55		
(Kruggel 2006)	F	145	24	670	640	1.05	-5.8%	-9.0%
	M	145	24	710	700	1.01		
(Luders et al. 2002)	F	50	24	740	360	2.06	-10.3%	-15.4%
	M	50	25	820	420	1.95		
(Good et al. 2001)	F	200	34	747	395	1.89	-10.4%	-13.9%
	M	265	31	829	454	1.83		
(Sowell et al. 2007)	F	86	33	744	444	1.68	-12.6%	-15.4%
	M	90	31	844	518	1.63		
(Lemaitre et al. 2005)	F	331	70	530	430	1.23	-9.0%	-13.0%
	M	331	70	580	490	1.18		
No rescaling of brain images, images measured in native space								
(De Bellis et al. 2001)	F	57	12	768	420	1.83	-10.3%	-16.2%
	M	61	12	851	494	1.72		
Present study	F	100	22	579	435	1.33	-9.5%	-16.8%
	M	100	22	637	515	1.24		
(Luders et al. 2005)	F	30	24	640	470	1.36	-11.8%	-15.7%
	M	30	25	720	550	1.31		
(Gur et al. 1999)	F	40	25	639	433	1.48	-7.2%	-22.7%
	M	40	27	687	544	1.26		
(Allen et al. 2003)	F	23	33	551	410	1.34	-9.5%	-16.1%
	M	23	32	606	482	1.26		
(Goldstein et al. 2001)	F	21	36	549	405	1.36	-5.5%	-12.1%
	M	27	39	580	457	1.27		
(Chen et al. 2007)	F	227	47	670	430	1.56	-9.9%	-15.1%
	M	184	47	740	500	1.48		

volume minimization in order to reduce transmission times (Zhang and Sejnowski 2000).

Corpus Callosum

The corpus callosum probably holds the record for reported sex differences (due in no small part to its ease of visualization and measurement). Virtually all studies have found that corpus callosum area increases with cerebral volume in both sexes but that women have corpora callosa that are larger than expected for brain size (Driesen and Raz 1995). In the Driesen and Raz review, 11 studies calculated proportional size. The median effect size was 0.26, which agrees quite nicely with the effect size of 0.33 found in the present study. The popular press has used this robust (although relatively modest) difference to support cultural assumptions about female superiority at multitasking. A recent Google search for sites mentioning corpus callosum, sex, and multitasking identified 532 web sites. Once again, however, this difference in proportional size can be attributed to sex differences in cerebral volume. In 1997, Jancke and associates reported that individuals with larger cerebral volume had smaller corpora callosa, regardless of sex. We also found this effect. Neither hierarchical multiple regression nor ANCOVA revealed a significant effect of sex after the effect of cerebral volume had been accounted for

(Tables 5 and 7). The fact that larger brains have relatively smaller callosa may be associated with the increased time involved in interhemispheric communication over long distances. Aboitiz et al. (1992) and Ringo et al. (1994) have speculated that the increased time involved in interhemispheric communication in large brains leads to an increased dependence on intrahemispheric rather than interhemispheric connections and increased hemispheric specialization.

Perisylvian Cortex

Many investigators have searched for sex differences in the perisylvian "language" areas. Most studies that have reported differences have used quite small samples but even very large studies can produce opposite results. In a post mortem study of 21 men and women, Harasty found that the proportional volumes of the planum temporale and the inferior frontal gyrus were larger in women than men (Harasty et al. 1997), although there was no mean hemispheric asymmetry in either sex. More recently 2 imaging studies have failed to replicate these findings. Vadlamudi et al. (2006) adapted Harasty's techniques in an MRI study of 42 children but failed to find any effect of sex on proportional volume of the planum temporale. In a study of the inferior frontal gyrus (Knaus et al. 2007) also failed to find sex differences in proportional volume. Two

recent studies have reported sex differences in the proportional volume of cortex on Heschl's gyrus. Rademacher et al. (2001) found that the volumes of cytoarchitecturally defined Brodmann's area 41 on Heschl's gyrus were proportionally larger in women, whereas an imaging study by Knaus et al. (2006) found that the gyrus defined by sulcal boundaries was proportionally larger in men.

In the present study, we found, like Rademacher, that the left and right Heschl's gyrus were relatively larger in women. We also found, like Harasty, that the planum temporale was relatively larger in women (although unlike Harasty, this difference was limited to the left hemisphere). We were not expecting to see these differences, given the difference between our measurement techniques and those employed in the rigorous post mortem studies of Rademacher and Harasty. We measure the surface area in a restricted region of the planum, a region chosen to maximize asymmetry (Leonard et al. 1993), whereas the volume measurement used by Harasty does not produce a leftward asymmetry, due, it is thought, to the left planum temporale being longer but thinner than the right (Harasty et al. 2003).

Because the sex difference in relative volume of these perisylvian regions appears to be somewhat robust to measurement technique, we investigated whether it varied with cerebral volume, like the sex differences in gray matter proportion and corpus callosum. Once again there was a reliable influence of cerebral volume, an influence many times larger than that of sex. There was a significantly negative relation between the proportional size of Heschl's gyrus and cerebral volume in both men and women. For the planum temporale, however, the relation between cerebral volume and left planar size differs in men and women (Table 3). In women, planar size does not depend on cerebral volume, whereas in men, it does. Thus, in women, as Harasty originally noted, the posterior perisylvian cortex is relatively larger than it is in men. Whether this difference depends on chromosomal sex, the influence of sex hormones, or sex-dependent experiences is an interesting question for future research.

Limitations and Measurement Issues

This study used a large normative sample of young adults that reflected the ethnic distribution of students at a large land grant university. The men and women did not differ in parental education, measured IQ, hand preference or reading skill. The sample was one of convenience, not one drawn using epidemiological techniques. In that regard it is typical of most studies of young adults. The average IQ was much closer to the mean of the US population than in many such studies, however.

Unlike most recent studies, images were not registered to a template but were processed and segmented into gray and white matter in what is referred to as "native" space, although the images had been realigned into standard planes. We made the decision not to register to a template because we suspected that brain size would emerge as an influential variable. When we assembled the data graphed in Figure 5, we were struck by the large effect that image registration had on gray/white ratios. Various methods of image registration were associated with gray/white ratios ranging from 1 to 2.5 in young adults. Ratios calculated from images segmented in native space, by contrast, had a much smaller range. Readers unfamiliar with digital image processing may wonder how

something as apparently solid as a gray/white boundary could vary so much among studies. It turns out that the sharp boundary visible to the naked eye (see Fig. 1) is an artifact created by our visual system, and not actually present in the data. Interestingly, however, the 5 studies reporting similar ratios each used a different tissue segmentation algorithm. This agreement is even more surprising, given a recent study by Clark et al. (2006) that reported a major impact of algorithm on segmentation accuracy. In their study, the optimal algorithm even differed for gray and white matter. The range of values in a sample of the published literature (Table 8) appears to depend more on type of template registration than segmentation technique. The image processing methods in the Clark study did not include template registration and we could not find a study that has compared volumes and gray/white ratios obtained when a data set containing multiple individuals was studied with different techniques.

For the size of its sample, this study is unusual in that it utilized the manual method of drawing surface areas rather than measuring lobar volumes or cortical thickness. Manual techniques are usually arduous to apply reliably because few structures have stable, easy to define boundaries. We have adopted the strategy of measuring perisylvian structures in the sagittal plane using proportionally sized slabs (standard positions) because of the consistency with which the frontal, temporal and parietal opercula can be visualized at these standard positions. As the measurements can be made very quickly (10–20 min per brain) it is possible to obtain multiple assessments in large samples. Although total volumes are not obtained, it can be argued that the surface area is a reasonable indicator of relative volume because of the invariant nature of columnar organization (Creutzfeldt 1977; Merker 2004). Although these measures may not be sensitive to cytoarchitectonic boundaries (Amunts et al. 2003) they indicate sulcal foldings that may reflect functional axonal connections (Van Essen 1997; Leonard, Eckert, Kuldau 2006).

If the goal of a study is to index individual differences, rather than absolute volumes, then there are advantages to a technique that can be rapidly applied to large samples. Some measure of validity for this type of measurement has been achieved, in that these measures of planum temporale (Leonard et al. 1996; Eckert et al. 2001; Chiarello et al. 2004) and pars triangularis (Gauger et al. 1997; Eckert et al. 2003; Leonard, Eckert, Givens, et al. 2006) predict cognitive and behavioral measures in children and adults. We also were able to replicate sex differences in the relation between total cerebral volume and language area volume with these surface area measures. Our interpretation of these sex differences differs from that of Harasty and Rademacher, however. Rather than speculating that the increased proportional size is the result of a sex-dependent selection for verbal skills, we suggest that this increased proportional size is one of many nonsex-dependent adjustments associated with less cerebral volume.

General Considerations

The idea that there is a general relation between total cerebral volume, and the relative proportion of gray and white matter components has a long history. In 1907, Kaes (cited in Seldon 2005) reported on a post mortem series of brains from individuals aged 3 months to 97 years of age. According to Seldon, Kaes found an inverse relation between cortical

thickness and the relative complexity of the myelinated fiber network. Cortical thickness decreased between childhood and the age of 23 years, whereas myelinated areas expanded until age 45. This protracted period of myelin development has recently been confirmed by Sowell et al. (2003) in a large imaging study. Seldon expanded on these observations to speculate that there is an inverse relationship between surface area and thickness (Seldon 2005). In this "balloon model" the cortex thins as the volume of the brain expands due to the expansion of white matter. The balloon model predicts that smaller brains will have relatively more cortex, as originally reported by Luders et al. (2002), and confirmed here. It appears possible that the relative proportion of neuropile and white matter in small and large cerebra is a simple result of physical forces and geometrical laws.

The finding that cerebral volume accounts for more variation in the size of brain subcomponents than sex would not surprise Barbara Finlay, a neuroscientist who first alerted the neuroscience community to the powerful influence of allometric scaling on species differences in brain conformation (Finlay and Darlington 1995). Finlay has received much criticism (Finlay et al. 2001) for her negative view of mosaic or modular evolution—the idea that brain subdivisions expand or contract independently as a result of selective pressures on particular functions. She speculates that evolution has chosen the simpler step of expanding brains in a general way, by global increases in the numbers of cell divisions early in development, providing an enlarged brain that is then available for functional colonization (Finlay et al. 2001). Our finding that cerebral volume accounts for substantial variance in a variety of measures is fully consistent with this view.

The fact that sex differences in gray/white ratio are largely a consequence of sex differences in cerebral volume leads inevitably to a consideration of these robust sex differences in size and how they relate to the equally robust sexual dimorphism in body size. The relationship between cerebral volume and body size does not appear to be simple. Cerebral volume differences are found during childhood well before boys demonstrate their pubertal accelerated growth spurt (NCHS 2007). In adults, Peters et al. (1998) summarizes data showing strong relationships between cranial capacity and height when the means for different ethnic groups are plotted against each other, but weak and inconsistent relations between these variables within individual samples. One possibility worth exploring is the relationship between maturation rate, cerebral volume, and body size. It is possible that individuals with faster maturation rates tend to have smaller brains and bodies, regardless of sex.

If natural selection has favored females with smaller brain and body volumes, it is not clear whether body size or brain size, or both were the targets of selection or how this sex difference is related to sex differences in reproductive strategy (Hrdy 1999). But regardless of the factors influencing the origin of sexual dimorphism, it remains the case that men and women confront similar cognitive challenges using differently sized neural machinery. Our findings imply that any sex-specific adaptations to overall brain size are not associated with large relative differences in the size of various cerebral regions. In this respect, our results suggest that brain size matters more than sex.

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Notes

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