Sex Differences in Temporo-limbic and Frontal Brain Volumes of Healthy Adults

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Sex differences have been observed in neurobehavioral measures and in neuroanatomic studies. Men and women differ in emotion processing, including perception, experience and expression, most notably reflected in greater male aggression. We examine temporo-limbic and prefrontal structures volumetrically in a large well-characterized sample of healthy adults, applying morphometric methods across cerebral regions that regulate emotions. Quantitative magnetic resonance imaging (MRI) was performed in 116 healthy adults, 57 men and 59 women, age range 18–49 years. We used reliable methods of region of interest identification to examine sex differences in volume of temporo-limbic and frontal regions. An automated tissue segmentation procedure was used to obtain separate measurements for gray and white matter. After correcting for cranial volume, men and women had identical volumes of amygdala and hippocampus, as well as dorsal prefrontal cortex. However, women had larger orbital frontal cortices than men, resulting in highly significant difference in the ratio of orbital gray to amygdala volume ($P = 0.002$). The larger volume of cortex devoted to emotional modulation may relate to behavioral evidence for sex differences in emotion processing.

Introduction

Sex differences in brain anatomy have been increasingly documented with methods for morphometric analysis of magnetic resonance imaging (MRI) data (Gur *et al*., 1991, 1999; Raz *et al*., 1997; Coffey *et al*., 1998; Courchesne *et al*., 2000; Nopolus *et al*., 2000; De Bellis *et al*., 2001; Goldstein *et al*., 2001). Quantitative MRI studies using algorithms for tissue segmentation suggested that men have higher white matter (WM) volumes than women (Filipek *et al*., 1994; Passe *et al*., 1997). Examining the tissue composition of the entire supratentorial space, Gur *et al*. (Gur *et al*., 1999) observed that women have a higher percentage of gray matter (GM) whereas men have a higher percentage of WM and cerebrospinal fluid (CSF). Volumetric MRI studies of specific regions have also suggested sex differences (Cowell *et al*., 1994; Schlaepfer *et al*., 1995; Raz *et al*., 1997; Resnick *et al*., 2000). Regional sex differences may shed light on the neurobiologic substrates of behavioral sex differences in healthy people and may provide insight into sex differences in behavior and hence the prevalence and severity of certain neurobehavioral disorders.

Sex differences in cognition have been well documented. Women perform better on verbal and memory tasks, whereas men excel in spatial tasks (Silverman *et al.*, 1996; Caplan *et al*., 1997; Collins and Kimura, 1997; McGivern *et al*., 1997; Seidlitz and Diener, 1998). Sex differences have also been observed in affect and emotion processing (Grossman and Wood, 1993; Bettencourt and Miller, 1996; Asthana and Mandal, 1998). Women perform better in speeded emotion recognition tasks (Natale *et al.*, 1983) and are more expressive (Asthana and Mandal, 1998; Kring and Gordon, 1998). Regarding emotional experience, women are more prone to clinical depression (Hartung and Widiger, 1998), mood fluctuations associated with phases of the menstrual cycle have been documented (Laessle *et al*., 1990; Fink *et al*., 1996; Van Goozen *et al*., 1996), and such phase-associated hormonal changes may relate to cognitive performance (Hampson, 1990, 1995). However, perhaps the most salient difference between men and women in emotional behavior, dwarfing any measurable differences in cognitive and emotion processing parameters, is the discrepancy in aggression (Björkqvist *et al.*, 1994; Wrangham and Peterson, 1996). For example, 82.4% of violent crimes are committed by males, and theft is the only crime where women constitute a substantial proportion of offenders (31.1%; Commonwealth of Pennsylvania, Uniform Crime Report, 1998).

Research on networks for regulating emotion have implicated the amygdala, hypothalamus, mesocorticolimbic dopaminergic systems, and projections to orbital and dorsolateral frontal, temporal and parietal cortex (Adolphs *et al*., 1996; Damasio, 1997, 1998; Rolls, 1999; LeDoux, 2000). Studies in patients with brain lesions support the role of these regions in emotion regulation (Cancelliere and Kertesz, 1990; Borod, 1993; Adolphs *et al*., 1994; Heilman, 1997). The amygdala is considered to be primarily involved in excitatory aspects of emotional behavior, while the orbital frontal region is implicated in modulation (Damasio, 1997; Rolls, 1999; Davidson *et al.*, 2000; LeDoux, 2000). Assuming that volume is associated with increased brain functional capacity (Gur *et al*., 1999), the lower incidence of violent behavior in women would lead to the prediction that women have higher orbital relative to amygdala volume than men.

The objective of this study was to examine whether sex differences in brain volumes associated with regulation of emotion may underlie the well established sex differences in emotional behavior. Toward this aim, we used highly reliable methods of region of interest (ROI) identification to compare healthy men and women on volumes of temporo-limbic and prefrontal regions. We obtained separate measurements for cortical gray and white matter using an automated tissue segmentation procedure. In view of the inhibitory role of orbito-frontal cortex and the lower rate of physical aggression in women, we hypothesized that women have higher ratios of frontal relative to amygdala volumes. In an attempt to reduce the effect of aging and concomitant hormonal changes, we have limited the study to adults younger than 50 years and included only premenopausal women.

Materials and Methods

Study Participants

A sample of 116 right-handed healthy adults, 57 men and 59 women, with an age range of 18–49 years, was recruited by advertisement in community newspapers. Participants underwent medical, neurological, psychiatric and neurocognitive evaluations to exclude for history of illness affecting brain function (Shtasel *et al*., 1991; Kareken *et al*., 1995).

All women were premenopausal. Men and women did not differ sociodemographically: age (mean ± SD), men 27.0 ± 5.7, women 25.0 ± 5.3; education: men 14.8 ± 2.2, women 14.8 ± 1.7; parental education: men 12.4 ± 2.2, women 12.3 ± 1.9; IQ: men 109.9 ± 13.5, women 106.9 ± 12.9; all $t < 1$. The study was performed after informed consent of each participant was obtained. The sample overlaps that reported in earlier publications where the present participants constituted a healthy comparison group (Gur *et al*., 1998, 2000a,b), and where sex differences in whole brain (Gur *et al*., 1999) and effects of aging (Gur *et al*., 2002) were examined. It consists of a random subsample where both subtemporal and subfrontal regions were identified and parcellated.

MRI

Image Acquisition

MRI scans were acquired on a GE Signa 1.5 T scanner (Milwaukee, WI). Axial spin-echo images were acquired using a repetition time (T_R) of 3000 ms; echo times (T_E) of 30 and 80 ms; in planes parallel to the canthomeatal axis with in-plane resolution of 0.859 × 0.859 mm; 5 mm slice thickness, and no gaps. For regional volumetric analysis, T_1-weighted images were obtained with a spoiled gradient-recalled pulse sequence (SPGR) with the following parameters: flip angle 35°; T_R 35 ms, T_E 6 ms, field of view 24 cm, NEX 1, 1 mm slice thickness and no interslice gaps. Transaxial images were acquired in planes parallel to the orbitomeatal line with in-plane resolution of 0.9375 × 0.9375 mm.

The T_1-weighted images were resliced along the anterior-to-posterior commissural (AC–PC) axis to standardize for head tilt. The axial MRI was rotated according to the AC–PC axis in the transaxial plane, the eyeballs in the coronal plane, and midline in the sagittal plane. Sagittal images were rotated so that the AC–PC axes were oriented to straight horizontal positions. No parenchymal lesions or skull abnormalities were evident neuroradiologically.

Tissue Segmentation

The brain volumes were extracted by automatically stripping scalp, skull and meninges using optimal thresholding and morphological operations on the image intensity and chamfer distance (Borgefors, 1986; Yan and Karp, 1994). The stripped MRI was segmented into GM, WM and CSF using an adaptive Bayesian algorithm (Yan and Karp, 1994), which models the image as a collection of tissue compartments with slowly varying mean intensity, plus white Gaussian noise [see Gur *et al*. (Gur *et al*., 1999)].

Regions of Interest

Analyses of whole brain volumes was performed with T_2-weighted images and yielded estimates of total GM, total WM and CSF. Only supratentorial tissue was included in the analyses, and the cerebellum and brain stem nuclei were excluded. This was done using standard guidelines as detailed in Gur *et al*. (Gur *et al*., 1991).

Temporo-limbic Subregions. The hippocampus and amygdala were drawn on the realigned sagittal series (Gur *et al*., 2000a) (see Fig. 1, top row). The hippocampus was defined as the GM structure lying on the lateral ventricle and bound inferiorly by the WM separating it from the parahippocampal cortex. Laterally and posteriorly it is bound by a WM region, the alveus, which separates the tail of the hippocampus from the atrium of the lateral ventricle, thus excluding the choroid plexus. On the more lateral slices, the anterior border is defined by the temporal horn of the lateral ventricle. On the more medial slices, a small strip of WM separates the hippocampus from the amygdala. The coordinates of the border established by the WM are maintained on those slices where there is no white strip present. The outline of the hippocampus is traced as it appears on each slice.

The drawing for the amygdala is performed on the sagittal plane but all three planes are used to determine the borders. The superior border is determined in two steps: first, the coronal slice cutting through the most inferior–anterior point of the temporal horn of the lateral ventricle is chosen from the sagittal plane. Then, on the coronal plane, the most lateral point of CSF where the chiasmatic cistern meets amygdala provides the linear superior border on the sagittal plane. The anterior border is determined by the caudal coronal slice in which the anterior commissure disappears and the third ventricle becomes continuous. This coronal slice is used as the anterior border on the sagittal plane. The inferior border of amygdala is determined by the axial slice on which the tip of the inferior horn of the lateral ventricle first appears. The posterior border of amygdala is drawn adjacent to the anterior border of hippocampus. Reliability was established by two raters who independently completed

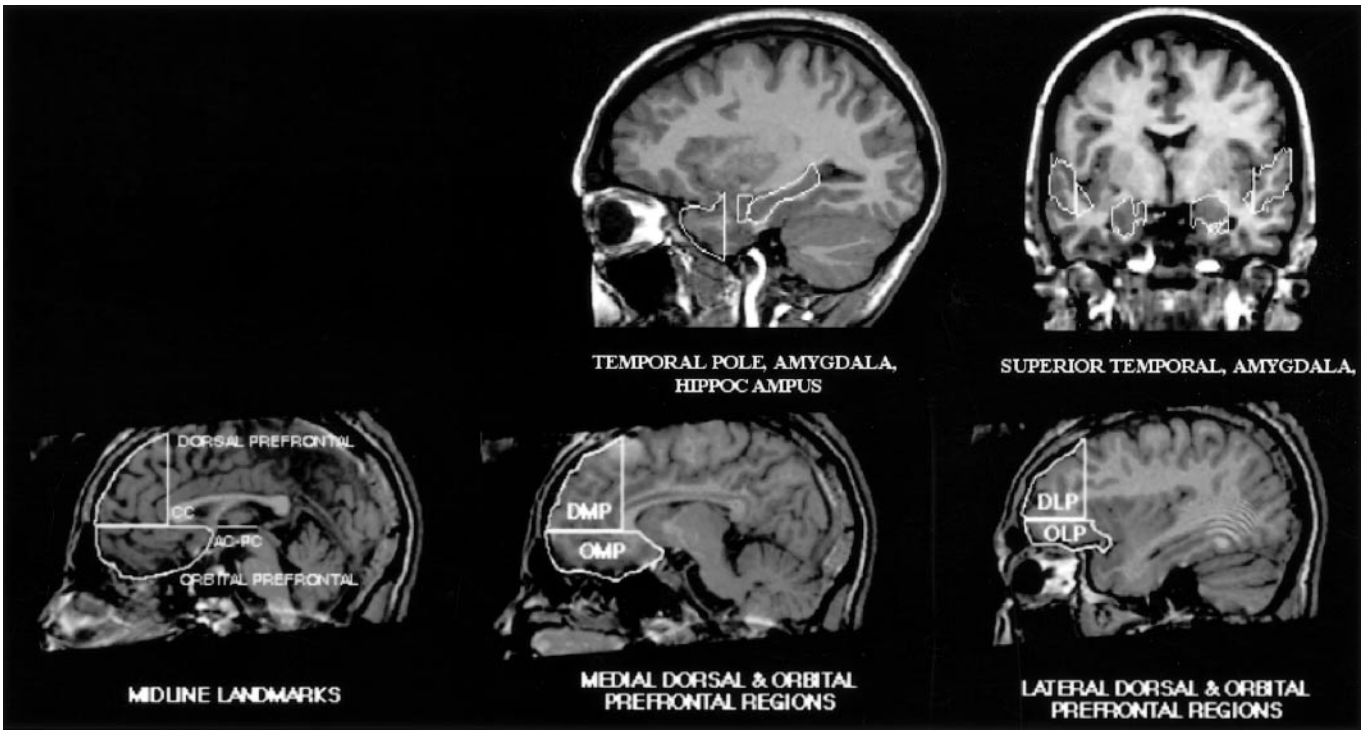

Figure 1. Illustration of ROI placement in temporal (upper row) and frontal (lower row) lobes.

Table 1
Means and SDs for the raw volumetric measures in men and women

	Men			Women		
Whole brain						
Total cranial	1365.2 ± 106.2			1195.1 ± 99.5		
GM	699.6 ± 66.7			642.7 ± 50.2		
WM	551.2 ± 71.1			452.1 ± 51.6		
Sulcal CSF	100.5 ± 34.1			87.9 ± 33.9		
Ventricular CSF	13.8 ± 5.4			12.0 ± 4.5		
	Left	Right	Total	Left	Right	Total
Regional						
Subtemporal						
Amygdala (AM)	1.94 ± 0.61	1.74 ± 0.61	3.68 ± 0.84	1.51 ± 0.41	1.37 ± 0.52	2.88 ± 0.90
Hippocampus (HI)	4.32 ± 0.85	4.60 ± 1.17	8.92 ± 1.72	4.08 ± 0.44	4.32 ± 0.44	8.40 ± 1.03
Prefrontal						
Laterodorsal						
GM (LDG)	15.27 ± 3.19	16.29 ± 3.12	31.56 ± 4.27	13.38 ± 2.35	14.74 ± 1.99	28.12 ± 5.88
WM (LDW)	11.13 ± 2.76	13.81 ± 3.04	24.94 ± 5.24	8.92 ± 2.35	11.48 ± 2.39	20.40 ± 5.35
Mediodorsal						
GM (MDG)	14.56 ± 2.53	14.14 ± 2.46	28.70 ± 4.12	12.52 ± 1.57	12.68 ± 1.91	25.20 ± 5.36
WM (MDW)	10.87 ± 2.38	10.22 ± 2.36	21.09 ± 4.76	8.77 ± 1.57	8.40 ± 2.15	17.17 ± 5.00
Latero-orbital						
GM (LOG)	8.25 ± 2.13	8.39 ± 2.31	16.64 ± 3.42	8.08 ± 2.18	8.06 ± 2.21	16.14 ± 2.82
WM (LOW)	3.71 ± 1.68	4.05 ± 1.95	7.76 ± 2.58	3.68 ± 1.48	3.86 ± 1.57	7.54 ± 1.82
Medio-orbital						
GM (MOG)	8.69 ± 1.98	8.27 ± 2.12	16.96 ± 3.58	8.04 ± 1.75	7.83 ± 1.72	15.87 ± 3.18
WM (MOW)	4.99 ± 1.70	5.20 ± 1.61	10.19 ± 2.90	4.51 ± 1.26	4.50 ± 1.36	9.01 ± 3.07

the temporal region drawings on the same 10 randomly selected cases. The intraclass correlations for the two subfields in each hemisphere ranged from 0.90 to 0.96.

Prefrontal Subregions. Subdivisions were derived with neuroradiologic and neuroanatomic input, using topographical triangulation and tissue segmentation techniques to maximize the precision and reliability of region delineation (Gur *et al*., 2000b) (see Fig. 1, bottom row). Prefrontal cortex was divided into dorsolateral, dorsomedial, and lateral and medial orbital sectors. Regions were drawn on the sagittal series with 3D visualization tools. The prefrontal region, for each hemisphere, extends from midline to the lateral cortical perimeters. The dorsal and orbital regions are separated by a line drawn at the level of the anterior commissure. This dividing landmark is used throughout the mediolateral extent of the frontal lobe. The inferior genu of the corpus callosum at midline marks the posterior border of the dorsal prefrontal region. The posterior border of the orbitomedial region is a line drawn from coordinates determined by the anterior tip of the corpus callosum and the inferior cortical border at the first appearance of caudate. Laterally, the posterior border of this region is a line drawn from the head of the caudate. The posterior border of the orbitolateral region is marked by the caudate and the insula. For both dorsal and orbital regions, an axial view of the gray–white segmented image is used to determine the border between the medial and lateral regions; they are divided by the medialmost aspect of cortical GM, which runs along the transverse orbital sulcus at the slice superior to the last view of the medial orbital sulcus.

The dorsal prefrontal region includes the frontal pole and frontomarginal, superior frontal, and anterior sections of the middle and inferior gyri; portions of the anterior cingulate may also be included at midline. The lateral portion of the dorsal region includes the lateral aspects of Brodmann's areas 8, 9, 45, 46, and dorsolateral aspects of 10. The medial portion of this region corresponds to the medial aspects of 8 and 9; dorsal portions of 32 and 24; and dorsomedial aspects of 10. The orbital prefrontal region includes the rectal, medial orbital and suborbital gyri, the ventral portion of the mesial superior gyrus, and the anterior, posterior and lateral orbital gyri. The lateral portion of the orbital region includes 47, lateral portions of 11, and inferolateral portions of 10. The medial portion of the orbital region corresponds to 12, 25, medial 11, inferomedial 10, and ventral 32 and 24. To establish reliability, two raters independently parcellated 10 randomly selected cases. The unbiased intraclass correlations for the four sectors in each hemisphere for GM and WM ranged from 0.88 to 0.98.

Data Analysis

To evaluate sex differences regionally, cranial volume was entered as a covariate in a sex × region Generalized Estimating Equations (GEE) model (SAS¨ GENMOD procedure). The GEE procedure was preferred over the more traditional repeated measures analysis of variance (ANOVA) principally because the ANOVA model makes the sphericity assumption about the variance structure. This assumption is often not met and the ANOVA model cannot accommodate generic correlation structures. GEE is a more recent methodology for the analysis of longitudinal or clustered data, and allows for many correlation structures among the values, including the ability to estimate this correlation structure rather than make assumptions (Diggle *et al*., 1994; Zeger and Liang, 1986). Finally, this model can be fit without any imputation of missing data points and without deleting subjects with some data missing.

For a direct test of the hypothesis that women have higher modulatory relative to excitatory neuronal volume in the emotion processing circuitry, the ratio of orbital to amygdala (OAR) volume was calculated for each participant. The hypothesis that the distribution of the OAR is different for males and females was tested using a generalization of the Fisher's exact test for contingency tables larger than 2 × 2 (Mehta and Patel, 1983). The categorical contingency table approach does require normality of the distribution of the OAR. The OAR variable was categorized into three ordered groups, representing low, medium and high OAR. These three categories were determined based on equally spaced intervals from the smallest to the largest observed OAR. This method was performed using STATA Version 6 (Stata Corporation, 1999).

Results

Means for men and women on all volumetric measures are presented in Table 1. As expected, men had higher cranial volumes and correspondingly higher brain and CSF volumes. Likewise, most regions had higher volumes in men.

The GEE analysis showed that cranial volume was a significant covariate, $\chi^2 = 375.97$, d.f. = 1, $P < 0.0001$. With cranial volume covaried, there was no main effect of sex but there was the expected main effect for region, $\chi^2 = 8154.94$, d.f. = 37,

$P < 0.0001$, indicating that the regions differed in volume. Regional specificity of sex differences was indicated by a sex × region interaction, $\chi^2 = 209.30$, d.f. = 37, $P < 0.0001$. The regional means for men and women, corrected for cranial volume, are shown in Figure 2.

The significant sex × region interaction justified follow-up GEE analyses within temporo-limbic and frontal regions to assist in identification of the sub-region differences. For temporo-limbic regions, a sex × amygdala versus hippocampus GEE was performed. Cranial volume was a significant covariate, $\chi^2 = 34.58$, d.f. = 1, $P < 0.0001$. There was the expected main effect of region, $\chi^2 = 679.18$, d.f. = 1, $P < 0.0001$, with higher volumes in the hippocampus (Fig. 2, left graph), and no other main effects or interactions were significant. Adding age as a covariate did not change the effects.

For the frontal lobe we used dorsal versus orbital, medial versus lateral, and gray versus white as within-group (repeated measures) factors. Again, the effect of the covariate of total intracranial volume was significant, $\chi^2 = 266.41$, d.f. = 1, $P < 0.0001$. However, even covarying for cranial volume there was a main effect of sex, $\chi^2 = 4.64$, d.f. = 1, $P = 0.0312$, with women having relatively higher frontal volumes. Main effects were also significant for dorsal versus orbital, $\chi^2 = 1668.32$, d.f. = 1, $P < 0.0001$, higher values for dorsal cortex, medial versus lateral, $\chi^2 = 27.65$, d.f. = 1, $P < 0.0001$, higher lateral than medial volumes, and gray versus white, $\chi^2 = 917.17$, d.f. = 1, $P < 0.0001$, with higher values for GM. Significant interactions were obtained for sex × dorsal versus orbital, $\chi^2 = 53.51$, d.f. = 1, $P < 0.0001$, with women having higher orbital volume than men relative to equal dorsal volumes (see Fig. 2, middle graph). There was also a significant higher order interaction of sex × dorsal versus orbital × medial versus lateral, $\chi^2 = 162.46$, d.f. = 8, $P < 0.0001$. This interaction indicated that the sex difference was particularly pronounced for orbital GM (Fig. 2, right graph).

The Fisher's exact test, which determines whether the distribution of the OAR across the three categories (low, medium and high) is the same for males and females, showed that indeed the distribution of OAR is different ($P = 0.002$) for males and females. Using four ordered categories for OAR, rather than three (Fig. 3), has no impact on this finding ($P = 0.003$). Note that only one male had an OAR higher than 7, compared with eight women with that ratio, while only three women had an OAR of <3.5, which was the ratio for about a quarter of the men.

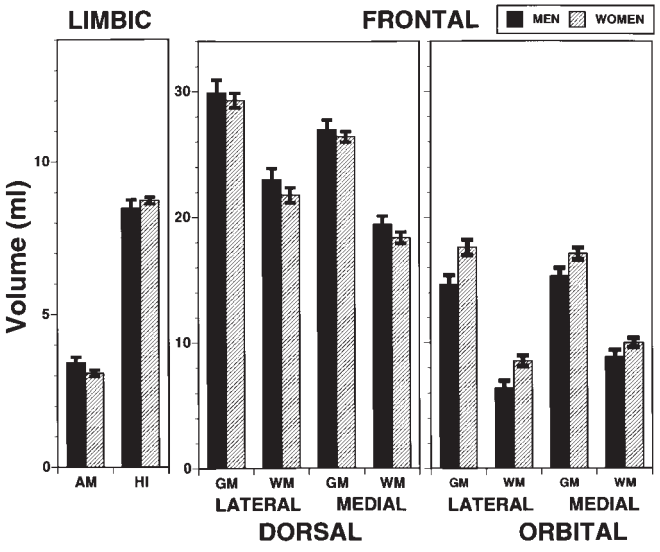

Figure 2. Regional means (±SEM) for men and women adjusted for intracranial volume.

Discussion

Following adjustment for intracranial volume, we observed sex differences in regional volumes in the frontal lobes where orbital frontal regions were relatively larger in women than in men. Although two MRI studies that measured the orbital frontal cortex failed to note a similar pattern, neither of these studies statistically adjusted the regional volumes for intracranial volume (Raz *et al.*, 1997; Szeszko *et al.*, 1999). The behavioral implications of women's relatively larger orbital frontal regions warrant further investigation in light of evidence for the critical role of the orbital frontal cortex in social behavior, emotional functioning and higher order cognitive skills, such as reasoning and decision making [for a review, see Fuster (Fuster, 1996)]. Indeed, reduced frontal volume has been associated with greater tendency toward psychopathy in healthy men (Matsui *et al.*, 2000) and in antisocial personality disorder (Raine *et al.*, 2000). Furthermore, the significance of larger orbital volumes can be interpreted relative to the volume of the amygdala whose input is modulated by this region (Damasio, 1997; Price, 1999; Rolls, 1999; Davidson *et al.*, 2000; LeDoux, 2000). We found that women, correcting for cranial volume, have equal volumes to men in temporo-limbic regions. Thus, the increased orbital volume relative to amygdala volume in women compared with men supports the hypothesis that women have greater tissue volume available for modulating amygdala input. This finding

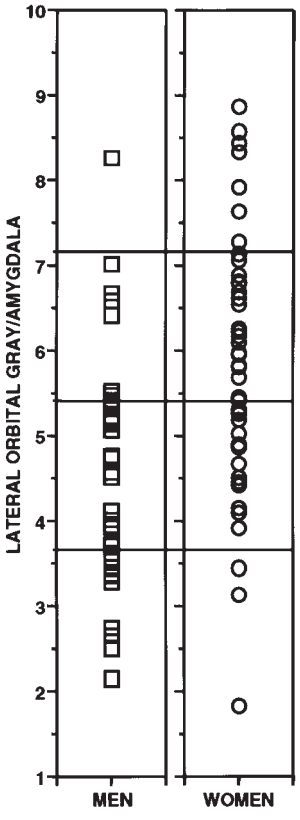

Figure 3. Scatterplots showing the distribution of the OARs in men (squares) and women (circles). Dashed lines indicate cut-offs for the four equally spaced intervals from the smallest to the largest observed used in the Fisher exact test.

may explain gender differences in emotional behavior, particularly aggression.

When interpreting the results of this study, there are several methodological limitations that must be considered. First, the *in vivo* MRI methods used in the current study cannot clarify the specific neurohistological processes that account for the observed volume differences. Neuronal bodies, neuronal size, or dendritic arborization are all potential sources of volume differences. Secondly, our regional analysis did not include the entire cerebrum. Future studies could include analysis of additional ROIs such as regions of the parietal lobe and infratentorial structures. Finally, the link between sex-related neuroanatomical differences in the temporo-limbic and prefrontal regions and cognitive and emotional functioning merits direct examination.

Nonetheless, the sex difference we have observed in the ratio of orbital to amygdala volume is quite marked. It is noteworthy that only five men had values in the range recorded in over half the women, and conversely only a handful of women had ratios as low as seen in about half the men. It is likely that such a neuroanatomical difference will have functional significance. While environmental and cultural factors undoubtedly contribute to sex differences in aggression, the existence of such marked neuroanatomical differences in brain structure related to emotion regulation warrants systematic effort to link emotional behavior to neural substrates. These anatomic differences also need to be considered when interpreting functional neuroimaging studies. Finally, animal studies may help determine whether these sex differences exist in other species and relate to differences in emotional behavior.

Notes

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