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Sex-specific alterations of cortical morphometry in treatment-naïve patients with major depressive disorder

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Major depressive disorder (MDD) shows sex differences in terms of incidence and symptoms, but the neurobiological basis underlying these sex differences remains to be clarified. High resolution T1-weighted Magnetic Resonance Imaging (MRI) scans were obtained from 123 non-comorbid treatment-naïve individuals with MDD and 81 age-, sex-, and handedness-matched healthy controls (HCs). MRI data were preprocessed with FreeSurfer software and four cortical measures were extracted: cortical thickness (CT), surface area (SA), cortical volume (CV), and local gyrification index (LGI). We tested for both sex-specific and sex-nonspecific patterns of cortical anatomic alterations. Regardless of sex, individuals with MDD showed significantly higher LGI in posterior cortex relative to HCs. Significant sex-by-group interactions were observed, and subsequent post-hoc analyses revealed that female individuals with MDD showed significantly lower SA in left ventrolateral prefrontal cortex (vlPFC), lower CV in right rostromedial prefrontal cortex (rmPFC), and higher LGI in left visual cortex compared with sex-matched HCs, whereas the opposite patterns of significant effects were seen in male individuals with MDD relative to their sex-matched HCs. Thus, sex-nonspecific and specific morphometric differences from HCs were found in posterior cortex, while in PFC alterations were highly sex-specific early in the illness course. This may involve sex-specific alterations in brain development or processes related to illness onset. These findings highlight the presence and regional distribution of generalized as well as sex-specific alterations of brain neurobiology in MDD.

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INTRODUCTION

Prominent sex differences in illness incidence rates and symptoms in major depressive disorder (MDD) are well established [1–3]. Female individuals with MDD have been reported to show more hypersomnia, hyperphagia, anxiety, psychomotor retardation, and weight gain, while male individuals with MDD show more psychomotor agitation, violence, irritability, substance abuse, somatic complaints, and risky behavior [1]. While previous studies reported sex differences in individuals with MDD in gene-expression, and in endocrine and metabolic systems [3–6], the neurobiological mechanisms underlying sex differences in MDD at the level of brain systems remain relatively undetermined.

Structural brain abnormalities in MDD have been widely reported in prefrontal-limbic circuitry, in regions including ventromedial prefrontal cortex (vmPFC), dorsomedial prefrontal cortex (dmPFC), and hippocampus [6–10]. Cortical morphometric abnormalities (especially in PFC) reported from individuals with longer-term MDD can be different from those seen in early-course individuals with MDD, potentially as a result of effects of treatment, chronic stress, and illness progression [11, 12]. Some sex-specific neuroanatomic alterations have been described in ventral and medial PFC regions that are important in emotion processing, motivation, and decision making [13, 14]. A voxel based morphometry (VBM) study reported smaller gray matter volume (GMV) in bilateral middle temporal gyrus and left vmPFC selectively in 29 males with MDD, whereas smaller GMV in the left dmPFC and lingual gyrus was seen in 53 females with MDD (60 patients were drug-naive and 22 had been medication-free for at least 3 months), compared with sex-matched healthy controls (HCs) [15].

To date, there have not been sufficiently powered studies to comprehensively investigate sex differences in different specific brain morphometric features in treatment naïve individuals with MDD, in whom illness-related anatomic features can be examined with reduced risk that confounds such as illness duration and medication effects would impact findings. Compared with sex-matched HCs, 16 medication-naïve females with MDD demonstrated smaller GMV in limbic regions, and 13 medication-naïve male patients showed smaller GMV mainly in striatal regions [16]. One study reported increased cortical thickness (CT) in rostral middle frontal gyrus selectively in 24 females with MDD (in mixed medication states), whereas increased CT in the left caudal anterior cingulate cortex (ACC) was seen in 9 male patients, compared with sex-matched HCs [17]. A more comprehensive summary of this literature is presented in Supplementary Table S1.

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Table 1. Demographic and clinical features of the treatment-naïve individuals with MDD and HCs.

	MDD ($N = 123$)	HC ($N = 81$)	*P* values
Age (years)	32.4 (11.3)	33.6 (10.8)	0.440
Female	32.7 (11.8)	35.2 (11.1)	0.127
Male	30.4 (12.1)	30.9 (7.4)	0.476
Sex (female/male)	78/45	51/30	0.948
Education level	–	–	0.534
Middle school and lower			–
Female	19	20	
Male	9	13	
High school			
Female	20	4	
Male	9	3	
University and higher			
Female	39	27	
Male	27	14	
ICV (cm^3)	1476.8 (139.2)	1470.5 (131.2)	0.742
Female	1482.5 (136.8)	1454.1 (115.1)	0.163
Male	1465.8 (158.3)	1499.3 (130.4)	0.378
Age of onset (years)	30.8 (11.5)	NA	–
Female	31.7 (11.3)		0.393
Male	29.8 (11.8)		
Illness durations (weeks)	29.7 (28.8)	NA	–
Female	22.8 (21.8)		0.207
Male	29.3 (29.7)		
HAMD scores	25.8 (5.4)	NA	–
Female	27.7 (5.4)		0.008**
Male	25.6 (5.3)		
Anxiety/ somatization scores	7.6 (2.1)	NA	–
Female	9.2 (1.3)		<0.001***
Male	7.5 (1.9)		
Weight change	0.9 (0.8)	NA	–
Female	0.9 (0.8)		0.268
Male	0.8 (0.7)		
Cognitive disturbance scores	4.9 (2.0)	NA	–
Female	4.9 (1.8)		0.660
Male	5.1 (2.3)		
Psychomotor retardation scores	8.3 (1.8)	NA	–
Female	8.9 (1.1)		0.026*
Male	8.2 (1.8)		
Sleep disturbance scores	3.7 (1.8)	NA	–
Female	3.8 (1.8)		0.914
Male	3.9 (1.8)		
HAMA scores	24.5 (9.1)	NA	–
Female	24.1 (9.0)		0.214
Male	25.9 (9.0)		

Data were presented as means (standard deviation), except for education level was presented as the number of people. Anxiety/somatization: HAMD 10, 11, 12, 15, 17; Weight change: HAMD 16; Cognitive disturbance: HAMD 2, 3, 9; Psychomotor retardation: HAMD 1, 7, 8, 14; Sleep disturbance: HAMD 4, 5, 6.

MDD major depressive disorder, *HCs* health controls, *R* right, *L* left, *HAMD* Hamilton depression scale, *HAMA* Hamilton anxiety scale, *ICV* intracranial volume, *NA* not applicable.

*$p < 0.05$; **indicated $p < 0.01$; ***indicated $p < 0.001$.

For these reasons, a study of neuroanatomic features in treatment-naïve individuals without psychiatric or systemic medical comorbidities may be informative about the location and specific anatomic features of potential sex-related differences of brain anatomy in individuals with MDD.

Relative to studies only examining regional brain volumes, a more comprehensive examination of sex-specific abnormalities of cortical morphology in MDD including CT, surface area (SA), cortical volume (CV), and local gyrification index (LGI) may advance understanding of sex-differences, as these features are influenced by distinct evolutionary, neurodevelopmental and genetic factors [18–20]. CT primarily reflects the number of neurons within a cortical column, SA is related to the number of cortical mini-columns, and the LGI reflects the degree and pattern of cortical folding during brain maturation. The widely used CV measure reflects a combination of CT and SA, which have distinct neurobiological significance [18, 20, 21].

In the current study, we tested for sex differences in cortical morphometric alterations in a relatively large sample of non-comorbid, treatment-naïve individuals with early-course MDD to identify sex-related deviation in cortical metrics in MDD patients relative to controls to take typical sex differences into account. These cohort features are important, because drug treatment, comorbid illness and illness duration can variably impact brain morphometry and confound measurement of illness-related features in case-control studies. We hypothesized that female and male individuals with MDD would show different alterations of volume in ventral and medial subregions of PFC, with measures of CT and SA used to advance understanding of the causes of volumetric alterations.

MATERIALS AND METHODS

Participants

The study was approved by the Research Ethics Committee of West China Hospital, Sichuan University, and written informed consent was obtained from all participants. One hundred and twenty-three individuals with MDD (78 females and 45 males) were recruited from the Mental Health Center, West China Hospital, Chengdu, China. MDD diagnoses were determined by two experienced psychiatrists independently using the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID). The 17-item Hamilton Depression Scale (HAMD-17) was used to evaluate the severity of depression in individuals with MDD, which provided a total score and five syndrome scores comprised of different HAMD items related to anxiety/somatization (HAMD 10, 11, 12, 15, 17), weight change (HAMD 16), cognitive disturbance (HAMD 2, 3, 9), psychomotor retardation (HAMD 1, 7, 8, 14), and sleep disturbance (HAMD 4, 5, 6) [22, 23]. The 14-item Hamilton Anxiety Scale (HAMA-14) was used to evaluate anxiety severity. Both rating scales were completed on the same day as magnetic resonance imaging (MRI) scanning. All participants were native Han Chinese and right-handed as determined using the Edinburgh Handedness Inventory.

Inclusion criteria for individuals with MDD were as follows: (1) aged 18–65 years; (2) met the DSM-IV diagnostic criteria for MDD; (3) naïve to all psychiatric treatments, including medications, psychotherapy, and neuromodulation therapy; (4) total HAMD-17 score ≥18 (moderate depression); (5) no comorbid Axis I psychiatric disorder; (6) no history of heart disease, major systemic illness or neurological disease; (7) no history of drug abuse or dependence; (8) no MRI scanning contraindications; and (9) no pregnancy or lactation. The mean illness duration was approximately 6 months in both males and females with MDD (Table 1).

Eighty-one HCs (51 females and 30 males) were recruited from the local area via internet advertisements, and were screened by two psychiatrists independently to exclude individuals with history of any Axis 1 disorder using the SCID (non-patient version). HCs were excluded if they had a first-degree relative with a known history of psychiatric illness. There was no significant difference between individuals with MDD and HCs in sex ratio ($\chi^2 = 0.004$, $p = 0.948$). The sex-matched individuals with MDD and controls did not differ in age or intracranial volume (ICV) ($p > 0.05$, Table 1).

MRI data acquisition

All participants were scanned on a 3T MRI scanner (Trio Tim, Siemens AG, Erlangen, Germany) with an eight-channel phased array head coil. High-resolution, T1-weighted images were obtained with a magnetization-prepared rapid gradient-echo sequence with the following acquisition parameters: repetition time (TR) = 1900 ms, echo time (TE) = 2.5 ms, inversion time (TI) = 900 ms, flip angle = 9°, matrix = 256 × 256, field of view = 256 × 256 mm^2, number of slices = 176, and slice thickness = 1.0 mm. Foam padding was placed around the head to reduce head motion. Soft earplugs were used to reduce scanner noise. Images were visually inspected by a radiologist immediately after acquisition, and individuals with visible head movement artifact were immediately rescanned.

Image processing

T1-weighted images were processed using FreeSurfer software (version 6.0) (http://surfer.nmr.mgh.harvard.edu/) with the standard recon-all stream. Briefly, image processing procedures included skull-stripping, transformation to Montreal Neurological Institute (MNI) space, segmentation of gray/white matter, intensity normalization, tessellation of the white matter and gray matter boundary, topology correction, surface deformation and inflation, surface atlas registration, surface extraction and gyral and sulcal labeling [24–27]. The outputs were inspected following standard quality control procedures described in the FreeSurfer tutorial. Two individuals with MDD with skull strip errors were fixed manually and re-run. In addition, a measure of ICV was extracted.

Cortical morphometry measurements

CT was defined as the closest straight-line distance between the pial surface and the gray/white matter boundary [25]. SA for each vertex was obtained by calculating the average area of the surrounding tessellated triangles on the pial surface [28]. CV was obtained by calculating the volume of tissue between the pial surface and the gray/white matter boundary [29]. Local cortical gyrification was quantified by the three-dimensional LGI. LGI was obtained by calculating the ratio of the amount of cortex within sulcal folds relative to that on the cortical surface within a 25 mm spherical region [20]. Vertex-level CT, SA, CV, and LGI of each subject were projected onto a targeted and normalized surface ("fsaverage").

Statistical analysis

Statistical analyses of cortical morphometrics were conducted with the Query, Design, Estimate, Contrast (Qdec) module in FreeSurfer (http://www.freesurfer.net/fswiki/Qdec). First, the CT, SA, and CV maps were smoothed with a Gaussian kernel of 10 mm full width at half maximum. The LGI map was not smoothed due to the intrinsic smoothness of its measurement. Second, a general linear model (GLM) was used to test for main effects of diagnosis and sex-by-diagnosis interactions on CT, SA, CV, and LGI in a vertex-by-vertex manner, with diagnosis and sex as fixed factors, and age and ICV as covariates. A Monte Carlo simulation was used to correct for multiple hypothesis testing, with 10,000 iterations, cluster-forming $p < 0.01$ and cluster-wise probability (CWP) < 0.05 [30, 31]. A Bonferroni correction method was used to further correct Type 1 error rate for the analysis of four GLMs independently (CT, SA, CV, LGI) and a threshold of CWP < 0.00625 two-tailed threshold for significance was used. Clusters with significant sex-by-diagnosis interactions on cortical morphometrics were defined as regions of interest (ROIs) and mean cortical measurements within each cluster was extracted for post hoc pairwise comparisons (with least significant difference correction) and correlational analyses.

To examine the relationship between brain regions with significant sex-by-diagnosis interactions and clinical features, mean cortical measurements within each cluster were extracted and partial correlation analyses were conducted with age and ICV controlled. To determine whether brain-behavior relations were different between male/female individuals with MDD, correlation coefficients were converted to *z* scores with Fisher's r to z transformation, and compared with *t*-tests for differences in correlations between groups. A false discovery rate (FDR) correction was applied to correct for multiple comparisons in exploratory correlational analyses between brain measures and clinical features.

RESULTS

Demographic and clinical features

Sex-specific demographic and clinical features of the 123 treatment-naïve individuals with MDD (78 females and 45 males) and 81 HCs (51 females and 30 males) are presented in Table 1. HAMD scores were significantly higher in female than male individuals with MDD, and on HAMD anxiety/somatization and psychomotor retardation syndrome scores. The females and males with MDD did not differ in age of onset, illness duration, or HAMA scores (Table 1).

MDD related cortical alterations

Significant case-control differences between MDD and HC participants (irrespective of sex) were found in the left temporo-parietal junction (TPJ) and right lateral occipital gyrus (LOG) with similar elevated LGI in both sexes of individuals with MDD as compared with HCs (CWP < 0.00625, Table 2, Fig. 1). Notably, these deficits were located primarily in posterior neocortex. Other clusters identified in analysis of individual brain metrics that didn't survive Bonferroni correction for the four brain features examined are reported in Supplementary Table S2 for heuristic purposes.

Sex-specific cortical alterations in MDD

Significant sex-by-case-control group interactions were found in SA of left ventrolateral PFC (vlPFC), CV of right rostromedial PFC (rmPFC), and LGI of left visual cortex (VC) (CWP < 0.00625, Table 2, Fig. 2). Post-hoc analysis revealed that the females with MDD had significantly lower SA in the left vlPFC and lower CV in the right

Table 2. Clusters of significant main effects of diagnosis and sex-by-diagnosis interactions in treatment-naïve individuals with MDD and HCs.

Cortical morphometric	Cluster location	Direction	MNI coordinates (peak vertex)			Size (mm^2/mm^3)	CWP
			x	*y*	*z*		
Main effects of MDD (controlling for age, sex, and ICV)							
LGI	L temporo-parietal junction	MDD > HC	−42.6	−59.8	6.0	4934.14	<0.001[a]
LGI	R lateral occipital gyrus	MDD > HC	42.9	−76.6	−0.2	782.08	0.004[a]
Sex-by-diagnosis interactions (controlling for age and ICV)							
SA	L ventrolateral prefrontal cortex	–	−38.3	39.2	1.9	2016.22	0.004[a]
CV	R rostromedial prefrontal cortex	–	20.5	−6.7	52.5	4309.27	0.001[a]
LGI	L visual cortex	–	−12.4	−94.6	−5.1	1028.95	<0.001[a]

The unit of CV was reported as mm^3.

MDD Major depressive disorder, *HCs* Health controls, *MNI* Montreal Neurological Institute, *SA* surface area, *CV* cortical volume, *LGI* local gyrification index, *ICV* intracranial volume, *L* left, *R* right, *CWP* cluster-wise probability.

[a]Indicated Bonferroni level significance (CWP < 0.00625, corrected for four cortical metrics, two-tailed).

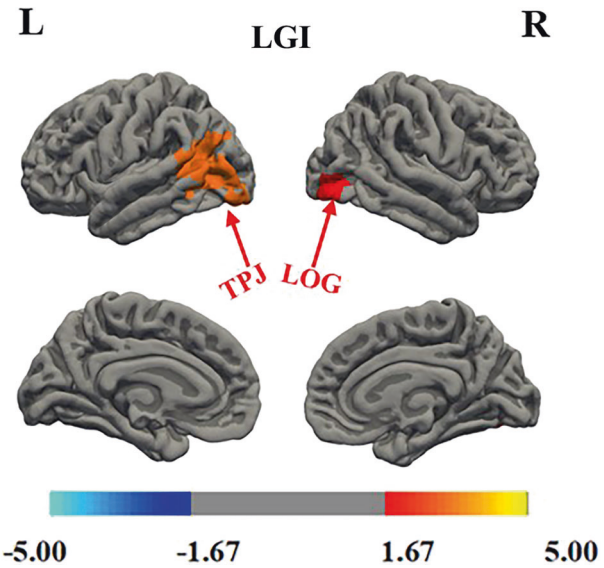

Fig. 1 Regions with significant case-control differences in local gyrification index in the 123 treatment-naïve individuals with MDD as compared with 81 HCs (cluster-wise probability < 0.00625, Bonferroni level significance). The color-bar for *p* values was on a logarithmic scale (log10) with a range of 1.67–5.00. L left, R right, MDD major depressive disorder, TPJ temporo-parietal junction, LOG lateral occipital gyrus.

rmPFC than their sex-matched controls, while males with MDD had significantly higher SA/CV of in these regions than their sex-matched HCs (Fig. 2A and Fig. 2B, post-hoc $p < 0.05$). In sex-by diagnosis interactions in left VC with LGI, post-hoc analysis showed that the LGI was higher in females than their sex-matched HCs and lower in males with MDD relative to their sex-matched controls (Fig. 2C, post-hoc $p < 0.05$). Other clusters identified in analysis of individual brain metrics that didn't survive Bonferroni correction for the four brain features examined are reported in Supplementary Table S2 for heuristic purposes. Exploratory heuristic analysis identified additional regions with alterations when case-control differences within sex were examined. Results of these analyses are presented in Supplementary Table S3 and Fig. S1. Additional analyses controlling for education level, severity of depression and age differences between males and females are reported in Supplementary Table S4–6. Findings of these additional confirmatory analyses were consistent with those of the primary analyses reported.

Clinical correlations

Post-hoc correlation analyses were conducted to examine relations between clinical measurements and identified MRI abnormalities. Higher LGI in the left VC was correlated with higher HAMD scores (Fig. 2C, $r = 0.361$, FDR-corrected $p = 0.005$) and anxiety/somatization scores (Fig. 2C, $r = 0.545$, FDR-corrected $p = 0.002$) in female individuals with MDD, while this alteration was not correlated with HAMD (Fig. 2C, $r = -0.005$, FDR-corrected $p = 0.973$) or anxiety/somatization scores (Fig. 2C, $r = -0.090$, FDR-corrected $p = 0.743$) in males with MDD. The correlations between LGI in the left VC and anxiety/somatization scores were significantly different between male and female individuals with MDD ($Z = -3.64$, FDR-corrected $p = 0.004$). No significant clinical correlations were observed in male individuals with MDD.

DISCUSSION

To the best of our knowledge, this is the first study to comprehensively investigate sex differences of cortical morphometry in a relatively large sample of treatment-naive individuals with MDD. Importantly, the patient cohort included non-comorbid treatment-naïve individuals with MDD, which reduces the potential influence of confounding effects related to illness course, prior treatment, and psychiatric comorbidities on our findings. We discovered both common and sex-specific alterations in cortical morphometry in individuals with MDD. Compared with the sex-matched HCs, individuals with MDD of both sexes had higher LGI in the left TPJ and right LOG.

Sex-related differences in cortical morphometry were also observed in the SA of vlPFC and CV of rmPFC, and in LGI of VC. Further analysis revealed that while females showed significantly lower of SA in the left vlPFC and lower CV in the right rmPFC, and higher of LGI in left PVC relative to their sex-matched HCs, the male individuals with MDD showed significant differences from their sex-matched controls in the opposite direction (higher SA of the left vlPFC, higher CV of the right rmPFC, and lower LGI in left VC). Thus, while all sex-nonspecific significant morphometric alterations in individuals with MDD were in posterior cortex, sex differences in the characteristics of illness-related alterations were identified in ventral and medial prefrontal circuitry that are important in emotion processing and are believed to be key regions of functional and anatomic abnormality associated with MDD. Significant correlations between clinical features and cortical morphometry were only observed in female participants.

Sex-specific alterations

Although lower SA in vlPFC and lower CV in rmPFC have been previously reported in sex-mixed MDD analyses [32–34], sex differences in these features have not been systematically examined previously. Some VBM studies of sex-specific alterations in MDD typically in smaller samples reported that male and female individuals with MDD show GMV alterations in different subregions of PFC as compared with sex-matched HCs [15, 16]. Our study demonstrated sex-differences from same-sex controls in the same subregions of PFC and VC. Importantly, male and female individuals with MDD showed the opposite pattern of divergence from their same-sex controls in each of these regions. Such differences might have affected findings of some prior work when sex was used as a covariate and individuals with MDD were analyzed as a group in case-control comparisons. Last, we note that some differences in our findings relative to prior studies may result from our recruitment strategy that limited confounding factors such as prior lifetime drug treatment for MDD, presence of other Axis I illnesses and course of illness effects that might have impacted some previous study findings.

The molecular mechanisms underlying sex-specific alteration in PFC morphometry are not known, and clarifying the mechanisms and timing of effects is not possible given our cross-sectional case-control design. However, possible explanations include differential brain maturational processes related to genetic susceptibility, and differences in neuroendocrine modulation of brain maturation and function between males and females. Key regulators of sex-specific gene networks underlying MDD have been identified that may impact resilience to stress [1], though their direct association with prefrontal anatomic features remains to be established. However, relevant findings consistent with sex-related brain differences in MDD have been reported, including demonstration that downregulation of the female-specific hub gene Dusp6 in mouse PFC mimicked stress susceptibility in females, whereas overexpression of the male-specific hub gene Emx1 in mouse PFC mimicked stress susceptibility in males [1]. Recently, a genetic study demonstrated that the long non-coding RNA LINC00473 (a primate-specific, neuronal-enriched gene) was downregulated in PFC in depressed females but not males, inducing abnormal stress resilience [35]. Also, glutamate-related genes have been reported to show increased expression in the dorsolateral prefrontal cortex of female individuals with MDD but decreased expression in male individuals with MDD [36]. Increased γ-aminobutyric acid

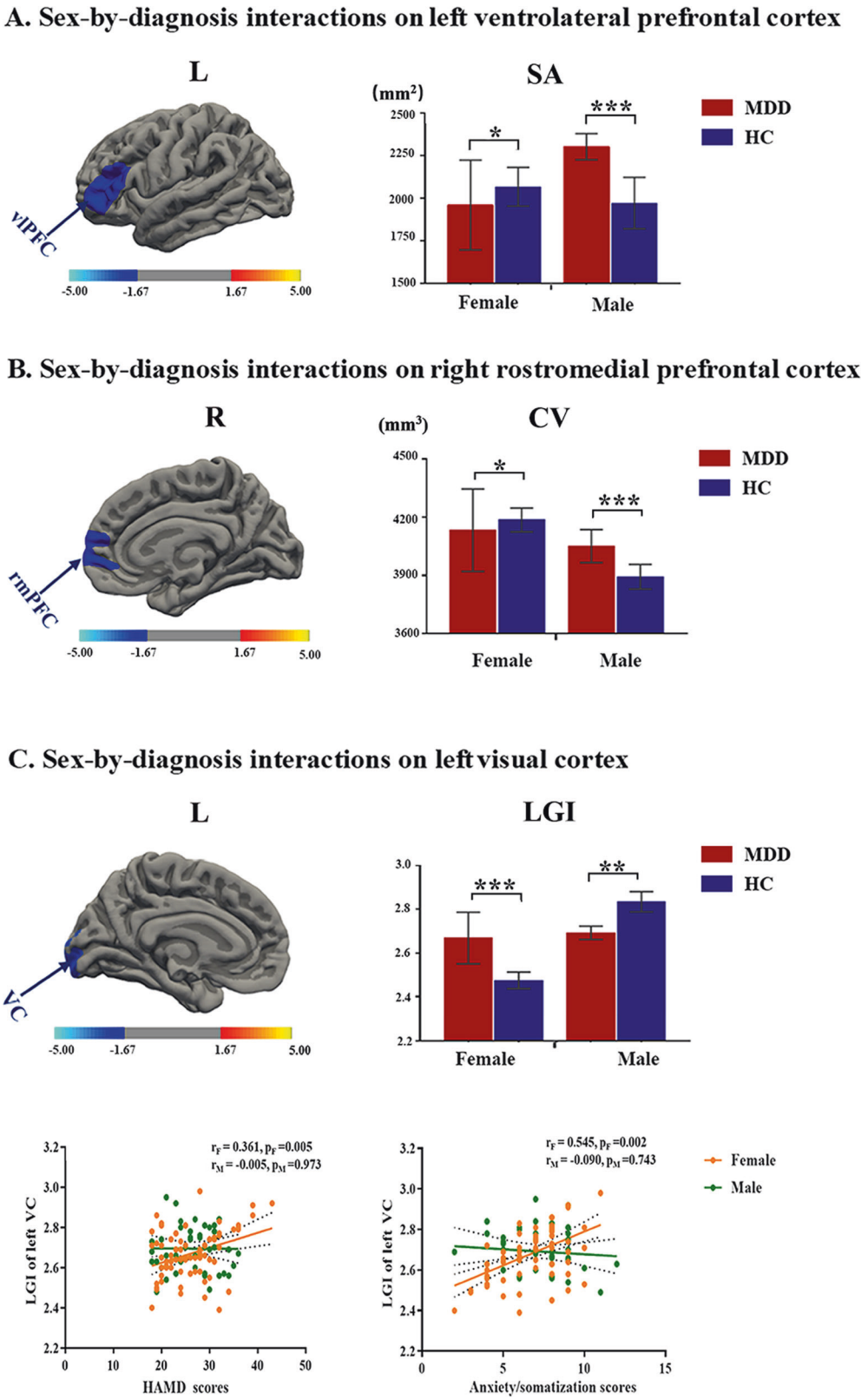

Fig. 2 Regions with significant sex-by-diagnosis interactions in cortical morphometry in treatment-naïve individuals with MDD and HCs. Significant sex-by-diagnosis interactions in the left vlPFC (**A**), right rmPFC (**B**), and left VC (**C**) between the treatment-naïve individuals with MDD and HCs (cluster-wise probability < 0.00625, Bonferroni level significance). These effects are illustrated by representative bar charts. The color-bar for *p* values was on a logarithmic scale (log10) with a range of 1.67–5.00. For the post-hoc analyses, * indicated $p < 0.05$; ** indicated $p < 0.01$; *** indicated $p < 0.001$. Scatterplots showing the correlations of LGI in the left VC with HAMD scores and anxiety/somatization scores in female and male individuals with MDD separately. *P* values for correlation analyses were presented with FDR correction. L left, R right, MDD major depressive disorder, HCs health controls, SA surface area, CV cortical volume, LGI local gyrification index, vlPFC ventrolateral prefrontal cortex, rmPFC rostromedial prefrontal cortex, VC visual cortex, F female, M, male.

(GABA)-ergic signaling reflected in parvalbumin expression in PFC may promote the onset of depression particularly in females [37]. While these genetic and neurochemical findings do suggest promising mechanistic explanations for the sex differences in prefrontal anatomy observed in individuals with MDD, experimental work to directly assess their relation to cortical morphometry alterations is needed to test these possibilities.

In addition to findings in PFC, sex-specific alteration was found in left VC, in which LGI was higher in females but lower in male individuals with MDD relative to their sex-matched controls. To our knowledge, no study has reported alterations of LGI in VC in individuals with MDD, although lower CV and decreased CT have been reported in mixed-sex analyses of individuals with MDD compared to HCs [7, 38]. The VC is responsible for processing visual information and feeding it forward for perceptual processing [39]. Our observation of LGI alteration in this region could be related to pre-attentive visual information processing impairments previously reported in individuals with MDD [40]. This abnormality might also contribute to altered facial emotion processing in MDD [41–43]. As higher LGI reflects long-range hypo-connectivity between brain regions [44], higher LGI in the VC observed in females with MDD in the current study may indicate hypo-connectivity between the VC and other brain regions involved in visual perceptual processing. Indeed, dysfunction of pre-attentive visual information processing has been reported previously to be sex-specific, only present in females with MDD [22].

We also observed that enhanced gyrification of VC was correlated with higher HAMD total scores and anxiety/somatization scores in female individuals with MDD, while these correlations were not observed in male individuals with MDD. As with PFC findings, the mechanism of atypical cortical gyrification in females is difficult to determine, but given the maturational timing of cortical gyrification it most likely is related to atypical early life brain maturation. Neurohormonal effects on brain maturation may be relevant both developmentally and through life. Sex differences in visual attention even from a young age are well established, and divergent development of this system may be associated with MDD in females in ways linked to anatomic features established in early childhood [45, 46]. Further work is needed to replicate our findings and test possible causes of this alteration.

Sex differences were found across multiple morphometric measurements, including SA, brain volume, and brain gyrification [47, 48]. Interestingly, our analyses showed sex-specific alterations in SA, CV, and LGI of ROIs but not in CT. Lower SA has been related to disturbances and delays in cortical maturation in individuals with MDD [7, 49, 50]. LGI is determined primarily prenatally and during the first years of life, reflecting maturation of cortical folding in neurodevelopment [51, 52]. Although also influenced by neurodevelopment, CT is genetically independent from SA and is determined by different neurobiological processes following an approximately linear developmental trajectory [29, 53, 54]. CV is more closely related to SA rather than CT [29]. Multiple factors including genetic and sex hormones influence impact sex differentiation of the brain [55–57], our finding that CT was not found to have sex-specific alterations may suggest sex-related genotypes that contribute to MDD impact neurobiological processes determining SA and LGI, but not CT. The current findings provide a profile of cortical morphometry characteristics in MDD that is sex-specific. Future research determining the cause of the identified alterations could advance to understand neurobiological mechanisms underlying sex-specific factors related to risk and expression of MDD.

MDD related alterations in posterior cortical regions

We found alterations of posterior cortical features in individuals with MDD, including, higher LGI in the left TPJ and right LOG, that did not differ by sex. The TPJ is known to be important for emotion perception which is altered in MDD [58, 59]. As higher LGI indicates more extensive cortical folding [20], the identified TPJ alterations suggest abnormal folding patterns in this region during early brain maturation that might contribute to disturbances of emotion regulation and risk for MDD [38, 60]. The LOG is an early visual processing region related to attention, feature-extraction, and shape recognition [61]. Abnormal folding patterns of LOG may contribute to reported alterations in visual processing in MDD [62]. These anatomic alterations were not sex-specific, suggesting that the mechanisms for these disturbances differs from those associated with PFC alterations in being independent from sex-related features.

Limitations

The current study has several features that merit consideration in interpretation of the results. First, our cross-sectional study investigating early course treatment-naïve individuals with MDD has advantages of avoiding confounds of treatment and chronic illness course in the assessment of cortical features. However, it is not clear whether conclusions drawn from the current study apply to depression after treatment or later in the illness course. Second, our cross-sectional design cannot answer questions of which of the brain anatomic alterations observed occurred early in life or emerged in relation to illness onset. Although prior studies suggest that our findings may be related to genetic factors given association of SA measures with genetic features in prior studies [7, 49, 50], and that gyrification findings are most suggestive of neurodevelopmental/early life processes [51, 52], direct linkages to genes and neurodevelopmental markers are needed to test and confirm these possibilities. Third, we did not investigate the potential impact of sex steroid levels on brain anatomy, either their maturational influences [63] or the impact of cyclic dynamic variation [64]. Such effects, as well as relations to immune activation, might be explored in future studies. Fourth, there was a greater number of female than males with MDD, so that we were better powered to identify clinical associations in females than males with MDD. In addition, we couldn't covary HAMD scores in our sex-by-group analyses where female had a higher HAMD scores than male. However, we replicated analyses with exclusion of females with highest HAMD scores and the results remains similar as presented in supplementary files. Fifth, the age range of individuals with MDD in our study is 18–65 years, so our findings are limited to midlife illness expression. The lifespan pattern of brain maturation in individuals with MDD remains to be clarified to better distinguish factors related to illness risk from factors related to illness onset. Last, we didn't obtain HAMD scores or other measures of emotion processing in HC, nor did we obtain additional measures of psychomotor agitation, irritability or facial emotion processing to link our anatomic findings more directly to these features in order to more fully understand the behavioral implications of our findings.

CONCLUSIONS

In this study, using a relatively comprehensive assessment of cortical morphometry in a sample of never-treated early course individuals with depression, we found both sex-specific and sex-nonspecific brain anatomic alterations in individuals with MDD. Sex-related differences were primarily in prefrontal cortex, while posterior abnormalities were typically similar in both sexes. Further, sex differences were most prominent in SA and gyrification metrics that most likely represent features of altered brain maturation. Sex-specific features observed in the current study could be related to early life brain development, however, further work is needed to establish the underlying mechanisms of these alterations.

These findings provide novel insight into the neurobiological substrate at the brain system level from a psychoradiological point

of view [65] to the well-documented sex differences in the incidence rates and clinical presentation of MDD and extend a literature that has primarily focused on clinical/behavioral features.

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AUTHOR CONTRIBUTIONS

XH and LZ formulated the research questions; XH and QG designed the study; JL, XH, WK, YH, LC, and HL acquired the data; XH, LZ, YG, and KL analyzed the data; XH, LZ, JAS, XH, and QG worked on data interpretation and wrote or revised the paper. All authors approved the final version to be published.

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COMPETING INTERESTS

Dr JAS consults to VeraSci. Other authors declare no competing interests.

ADDITIONAL INFORMATION

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