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Increased prefrontal and parietal cortical thickness does not correlate with anhedonia in patients with untreated first-episode major depressive disorders

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ABSTRACT

Cerebral morphological abnormalities in major depressive disorder (MDD) may be modulated by antidepressant treatment and course of illness in chronic medicated patients. The present study examined cortical thickness in patients with untreated first-episode MDD to elucidate the early pathophysiology of this illness. Here, we examined cortical thickness in patients with first-episode MDD ($N=27$) and healthy controls ($N=27$) using an automated surface-based method (in FreeSurfer). By assessing the correlation between caudate volume and cortical thickness at each vertex on the cortical surface, a caudate–cortical network was obtained for each group. Subsequent analysis was performed to assess the effect of anhedonia by the Temporal Experience of Pleasure Scale. We observed increased cortical thickness at the right orbital frontal cortex and the left inferior parietal gyrus in MDD patients compared with healthy controls. Furthermore, morphometric correlational analysis using cortical thickness measurement revealed increased caudate–cortical connectivity in the bilateral superior parietal gyrus in MDD patients. All changes were not related to anhedonia. These preliminary findings may reflect disorder manifestation close to illness onset and may provide insight into the early neurobiology of MDD.

1. Introduction

The neurobiological basis of major depressive disorder (MDD) is not fully understood. Extensive previous structural neuroimaging studies had reported volumetric changes in chronic medicated MDD patients at the anterior cingulate cortex (ACC) (Arnone et al., 2012; Du et al., 2012), the thalamus (Kempton et al., 2011; Arnone et al., 2012), the dorsolateral prefrontal cortex (DLPFC) (Bora et al., 2012) and the orbitofrontal cortex (OFC) (Kempton et al., 2011; Arnone et al., 2012). However, these studies usually recruited depressive subjects taking antidepressant medication, and the findings might be confounded by medication effects. Studies with unmedicated patients could better elucidate brain abnormalities independent from these potential confounds.

Several methods are available to measure morphological changes in the brain, including the manual volumetric region-of-interest (ROI) method and the automated voxel-based morphometry (VBM) method (Ashburner and Friston, 2000; Ridgway et al., 2008). Novel methodology has been developed to measure cortical thickness by calculating the distance between gray and white matter surfaces across the entire cortical mantle (Fischl and Dale, 2000). The surface-based estimates serve as more accurate indicators of the integrity of cortical cytoarchitecture, which is sensitive to neurodevelopmental and pathological changes and could reflect the size, density and arrangement of cells (Sowell et al., 2004). However, few studies have examined cortical thickness in patients with MDD and the results are inconsistent. Some studies reported reduced cortical thickness in the prefrontal regions (including the DLPFC and the OFC), the cingulate cortex, the temporal cortex, the parahippocampal regions and the insula in chronic medicated patients such as patients with diabetes and

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major depression (Ajilore et al., 2010), non-remitters (Jarnum et al., 2011) and elderly depressed patients (Lim et al., 2012). In contrast, other studies found significantly increased cortical thickness in the temporal pole (van Eijndhoven et al., 2013), the caudal anterior and posterior cingulate cortex (van Eijndhoven et al., 2013), prefrontal and parietal cortex (Qiu et al., 2014) in first episode medication-free MDD patients and in depressed youths (Fallucca et al., 2011; Reynolds et al., 2014). Recently, two longitudinal studies reported thinner posterior cingulate cortex in depressed non-remitters than in remitters at baseline and at follow-up scan (Jarnum et al., 2011) and increased cortical thickness in the left inferior frontal in patients MDD (Papmeyer et al., 2014). These findings raise the possibility that the increased cortical thickness at illness onset might represent a compensatory response to factors related to inflammation, and cortical thinning might be related to illness chronicity and poor clinical outcome in depressed patients. However, the existing evidence in early-course medication-naïve MDD patients is limited.

To further delineate the regional cortical thickness deficits of the cortex and their relationship, this study used morphometric correlational analysis to measure cortical thickness across the brain to provide information about changes in brain circuitry. This measure has been proposed as an alternative means of studying structural connectivity patterns between cerebral regions (Bullmore et al., 1998; McAlonan et al., 2005). Morphometric correlational analysis relies on the assumption that positive correlations indicate connectivity, as axonally connected regions are believed to have common trophic and maturational influences (Bernhardt et al., 2008). Indeed, previous studies reported that such correlational analyses reveal a similar pattern with white matter connections from diffusion tensor imaging studies (Lerch et al., 2006; He et al., 2007; Bernhardt et al., 2008) and thus this approach allows to assessment localization of alterations of brain networks in a diseased population. To date, only one study has used correlational analysis to examine cortical thickness in MDD. A broad coherent effect across several areas of the association cortex was found in first-episode MDD patients (Qiu et al., 2014). However, their measurements were restricted to the cortical mantle and did not assess cortico–subcortical circuits. Striatal–cortical connectivity has been implicated in the pathophysiology of MDD (Kober et al., 2008; Price and Drevets, 2010). Previous studies have generally focused on characterizing disruptions of ventral ("affective") striatal–prefrontal circuitry supporting emotional processes. Recent evidence, however, has emerged to suggest the presence of primary functional connectivity alterations of dorsal "cognitive" cortico–striatal circuits in depressed populations (Furman et al., 2011; Gabbay et al., 2013; Kerestes et al., 2015). The caudate, the main subregion of the dorsal striatum, mediates reward behaviors and pleasurable experience by dopaminergic neural pathways in MDD (Koob, 1996; Haruno et al., 2004). Neuroimaging studies have reported reduced caudate volume (Harvey et al., 2007; Kim et al., 2008; Pizzagalli et al., 2009), diminished response at the bilateral caudate during reward-related tasks (Pizzagalli et al., 2009; Smoski et al., 2009), as well as increased functional connectivity of the caudate with the cortex in MDD patients (Furman et al., 2011; Zhang et al., 2011; Liu et al., 2014). In our previous work, we also found that weaker caudate nucleus responses are associated with cost-benefit decision-making dysfunction in first-episode MDD patients (Yang et al.,in press). It is possible that the structural deficit of the caudate may be related to clinical symptoms such as anhedonia observed in MDD.

In the present study, we investigated cortical thickness, subcortical volumes and caudate–cortical correlations in untreated first-episode MDD patients to examine the brain abnormalities at the early stage of the illness. First, we compared whole brain morphometric measures including cortical thickness and volume of subcortical structures between MDD patients and healthy controls. Then, we took the caudate as a seed region to evaluate patterns of anatomical correlation between caudate volume and cortical thickness. Finally, we investigated the association between anhedonia and brain abnormalities. Based on the previous studies of prefrontal dysfunction in patients with MDD (Liu et al., 2014), we hypothesized that patients with first episode MDD would exhibit increased cortical thickness in the orbitofrontal cortex compared with healthy controls and these alterations are related to anhedonia as assessed by the Temporal Experience of Pleasure Scale. Given that extensive reciprocal connections exist between the caudate and the cerebral cortex, we also hypothesized that MDD patients would exhibit disrupted caudate–cortical connectivity involving the prefrontal and parietal regions.

2. Materials and methods

2.1. Participants

Twenty-seven first-episode, drug-naïve patients with MDD were recruited from the outpatient clinic of the Second Xiangya Hospital in Central South University. All the patients met the diagnostic criteria for MDD according to the Diagnostic and Statistical Manual, Fourth Edition (DSM-IV) (APA, 2000). Inclusion criteria were (1) DSM-IV first-episode MDD with no history of drug treatment; (2) currently experiencing an episode of depression with HAMD total score ≥ 20 on the 24-item Hamilton Rating Scale for Depression (HAMD) (Williams, 1988); and (3) a duration of illness of not more than 60 weeks. Exclusion criteria included (1) any history of psychotropic medication or psychotherapy; (2) current or history of MDD with psychotic symptoms; and (3) the presence of other Axis I diagnoses (including lifetime substance dependence and any substance use disorder in the past year), except anxiety disorders.

Twenty-seven healthy controls were also recruited from the community through advertisement. Healthy controls were free from any medical or neurological illness, and were screened using the Structured Clinical Interview for DSM-IV (SCID) (First, 2012) to ascertain the absence of psychiatric disorders. All participants were right-handed as assessed by the Annett Handedness Scale (Annett, 1970). The Central South University Institutional Review Board approved all procedures. A complete description of the study was provided to all participants, who gave written informed consent before the commencement of the study.

2.2. Clinical assessments

The Beck Depression Inventory (BDI) (Beck et al., 1961) is a 21-item scale that evaluates the severity of depression. The Chinese version used for the present study has been validated in Chinese samples (Wang et al., 1999). The internal consistency coefficient in the current sample was 0.83.

Anhedonia was assessed by the Chinese versions of the Snaith–Hamilton Pleasure Scale (SHAPS) (Liu et al., 2012) and the Temporal Experience of Pleasure Scale (TEPS) (Chan et al., 2010, 2012). The SHAPS was used to measure the state of anhedonia, whereas the TEPS was used to measure anticipatory and consummatory pleasure experience. The Chinese version of these scales has also been shown to possess adequate reliability in a previous study (Chan et al., 2012).

2.3. Data acquisition and preprocessing

Structural images from all participants were acquired on a 3-Tesla scanner (TrioTim, Siemens). The scanning parameters of

the T1-weighted three-dimensional magnetization-prepared rapid gradient-echo (MPRAGE) sequence were as follows: slice thickness = 1 mm, TE = 2.26 ms, TR = 2000 ms, flip angle = 8°, matrix size = 256 mm × 256 mm; 176 slices in sagittal plane, field of view (FOV) = 256 mm × 256 mm, voxel size = 1x1x1 mm^3. Images were inspected by experienced radiologists to exclude any incidental brain structural abnormalities.

For cortical reconstruction of the whole brain, the FreeSurfer imaging analysis suite (v5.1.0, http://surfer.nmr.mgh.harvard.edu/) (Dale et al., 1999; Fischl and Dale, 2000) was used. With this software, the T1-weighted images were registered to the Talairach space of each participant's native brain and the skulls were stripped. Images were then segmented into white matter/gray matter (WM/GM) based on local and neighboring intensities. The cortical surface of each hemisphere was inflated to an average spherical surface to locate both the pial surface and the WM/GM boundary. Cortical thickness was measured based on the shortest distance between the pial surface and the GM/WM boundary at each point across the cortical mantle. The regional thickness value at each vertex for each participant was mapped to the surface of an average spherical surface (Fischl et al., 1999). In addition, intracranial volumes (ICV) and volumes of subcortical structures (including the caudate, the putamen, the amygdala, the hippocampus, the thalamus and the nucleus accumbens) of each hemisphere were extracted from the automated parcellation (Fischl et al., 2004). Preprocessed results, including both the segmentation and parcellation were visually inspected before including into subsequent statistical analyses. The preprocessed images of two of the participants were unsatisfactory and were therefore excluded from further analysis.

2.4. Statistical analyses

First, we compared the patient and control groups on age, gender and estimated IQ (assessed by the Chinese version of the Wechsler Adult Intelligence Scale—Revised) (Gong, 1992), as well as the scores on self-reported scales by the Statistical Package for Social Sciences (SPSS v.24.0) software. The significance threshold was set at $p < 0.05$ (two-tailed).

Then, vertex-by-vertex whole brain cortical thickness comparisons were conducted in Qdec 1.4 using a general linear model (GLM). The cortical thickness images of each participant were smoothed with a Gaussian kernel of 15 mm full width at half maximum kernel (FWHM), and analyses were performed separately on the right and left hemisphere. Age, gender, and ICV were taken as covariates. The significance threshold was set at $p < 0.001$ (two-tailed, uncorrected). Only clusters with > 100 vertices were reported.

The volumes of subcortical structures, including the thalamus, the caudate, the putamen, the amygdala, the hippocampus and the nucleus accumbens, were also compared between the two groups using multivariate analysis of covariance (MANCOVA) in SPSS v.24.0, with age, gender and ICV as covariates. The significance threshold was set at $p < 0.05$.

Correlations between the volume of the caudate and cortical thickness of each vertex were conducted and the group differences were compared in Qdec. The significant differences in the association between caudate volume and cortical thickness between the MDD and control groups were reported. The threshold was set at $p < 0.001$ (two-tailed, uncorrected). Only clusters with > 100 vertices were reported.

Subsequent to both whole brain analyses of cortical thickness and caudate-cortical correlation, survived significant clusters were selected as regions of interest (ROI). The mean cortical thickness of each participant in each ROI was drawn manually and extracted in Qdec. We then calculated the correlations with their clinical variables (only for MDD patients) and self-reported scale scores (in both groups) in the SPSS. One-tailed partial correlation analysis was performed, with age, gender and ICV as covariates. The significance threshold was set at $p < 0.05$.

3. Results

3.1. Demographic and clinical characteristics

Table 1 summarizes the clinical characteristics and self-reported measures of the participants. There were no significant differences between the patient and the control groups in gender, age, years of education and IQ. The patient group had higher levels of state anhedonia (measured by the SHAPS), higher levels of trait anticipatory and consummatory anhedonia (measured by the TEPS) than healthy controls. The MDD group had higher levels of depressive symptoms (measured by the BDI) (all $ps < 0.001$).

3.2. Comparison of cortical thickness and subcortical volume

Vertex-by-vertex whole brain comparisons of cortical thickness showed that the MDD group had thicker cortices in the medial orbitofrontal cortex in the right hemisphere and the inferior parietal gyrus in the left hemisphere compared to controls. Details are summarized in Table 2 and Fig. 1.

We also compared subcortical volumes between the two groups, including the volume of the thalamus, the caudate, the putamen, the hippocampus, the amygdala and the nucleus accumbens in each hemisphere. No significant differences were found.

3.3. Caudate–cortical structural connectivity

Further to the group comparison on cortical thickness, we explored the group differences on the association between caudate volume and cortical thickness. The results showed that the two groups exhibited different caudate–cortical correlation pattern in the bilateral superior parietal gyri: positive correlations were found in MDD patients, but negative correlations were found in controls, suggesting increased caudate–parietal connectivity in MDD patients (See Table 3 and Fig. 2).

3.4. Partial correlation analysis

Table 4 shows partial correlations between the mean cortical thickness of the ROIs and clinical characteristics in the MDD group. We found that a longer duration of illness was associated with a thinner right medial orbitofrontal cortex ($r = -0.45$, $p = 0.026$). We also found that the BDI scores were positively correlated with cortical thickness of the bilateral superior parietal gyri (left: $r = 0.41$, $p = 0.023$; right: $r = 0.37$, $p = 0.039$). In contrast, no significant correlations were found in the healthy controls. We also did not observe any significant correlation between anhedonia and the four ROIs in both groups. Scatter plots of the significant correlations are presented in Fig. 3.

4. Discussion

In this study, we observed increased rather than reduced cortical thickness in early-course never-treated MDD patients in the right medial orbitofrontal cortex and the left inferior parietal gyrus compared with controls, while increased cortical thickness of the right medial orbitofrontal cortex was negatively correlated with duration of illness. Secondly, morphometric correlation analysis

Table 1
Demographic information and self-reported measures of the participants.

	Healthy controls ($N=27$)	MDD patients ($N=27$)	$t/\chi^2(df=52)$
Gender (M/F)	14/13	14/13	$\chi^2=0.00, df=1$
Age (years)	28.74 ± 7.93	28.59 ± 6.82	0.074
Education (years)	13.63 ± 2.66	14.26 ± 2.66	−0.87
Estimated IQ	114.59 ± 14.71	110.96 ± 19.32	0.77
SHAPS	21.11 ± 6.41	34.00 ± 6.03	−7.79***
TEPS	81.30 ± 12.25	63.52 ± 12.19	5.45***
TEPS-ANT	36.70 ± 6.16	29.85 ± 6.89	3.85***
TEPS-CON	44.59 ± 6.88	33.67 ± 6.89	5.73***
BDI	11.41 ± 10.09	33.19 ± 9.88	−8.02***
Course (month)	–	9.74 ± 7.08	
HRSD (24–item)	–	27.78 ± 4.78	–

Notes: BDI: Beck Depression Inventory; HRSD: The Hamilton Rating Scale for Depression; IQ: Chinese version of the Wechsler Adult Intelligence Scale—Revised; SHAPS: Snaith–Hamilton Pleasure Scale; TEPS-ANT: Temporal Experience of Pleasure Scale—Anticipatory Pleasure Subscale; TEPS-CON: Temporal Experience of Pleasure Scale—Consummatory Pleasure Subscale.
***$p < 0.001$.

found increased caudate–cortical connectivity in the bilateral superior parietal gyrus in MDD patients. These regions were positively correlated with BDI scores in patients with MDD. Finally, we did not observe any significant correlation between anhedonia and increased cortical thickness. These findings complement previous neuroimaging studies by demonstrating increased cortical thickness of the prefrontal and parietal cortices and caudate–cortical connectivity in first-episode, unmedicated MDD patients.

Our main findings are that patients with first-episode MDD have significantly increased cortical thickness in the right orbitofrontal cortex and the left inferior parietal gyrus compared with controls. Consistent with previous work (Qiu et al., 2014), our findings support the hypothesis that greater cortical thickness may reflect a compensatory mechanism related to inflammation or other aspects of the pathophysiology of depression. Although the reasons for the increased thickness of the neocortex in MDD are currently unclear, one possibility is that the early stage of illness may be characterized by glial pathology, which could increase cortical thickness due to hypertrophy of glial cells through compensatory mechanisms, but these compensatory mechanisms are unable to prevent the accumulation of extracellular glutamate in the long run, leading to volume loss in the chronic stage of MDD (Rajkowska and Miguel-Hidalgo, 2007; Dowlati et al., 2010). This idea is supported by the fact that increased thickness of the medial

Table 2
Clusters with significant difference between participants with MDD and HC.

Contrast	Hemisphere	Annotation	−log (p)	Talairach			Number of vertex	Size (mm^2)
				X	Y	Z		
MDD > HC	L	inferior PG	−4.08	−28	−64	29	723	337.59
	R	medial OFC	−3.63	8	15	−18	238	107.16

Notes: MDD: Major Depressive Disorder; HC: Healthy Control; OFC: Orbitofrontal cortex; PG: parietal gyrus. Whole brain group comparisons were conducted by Qdec with threshold $p < 0.001$, uncorrected. Clusters with vertices > 100 were shown. Age, gender, and ICV were taken as covariates.

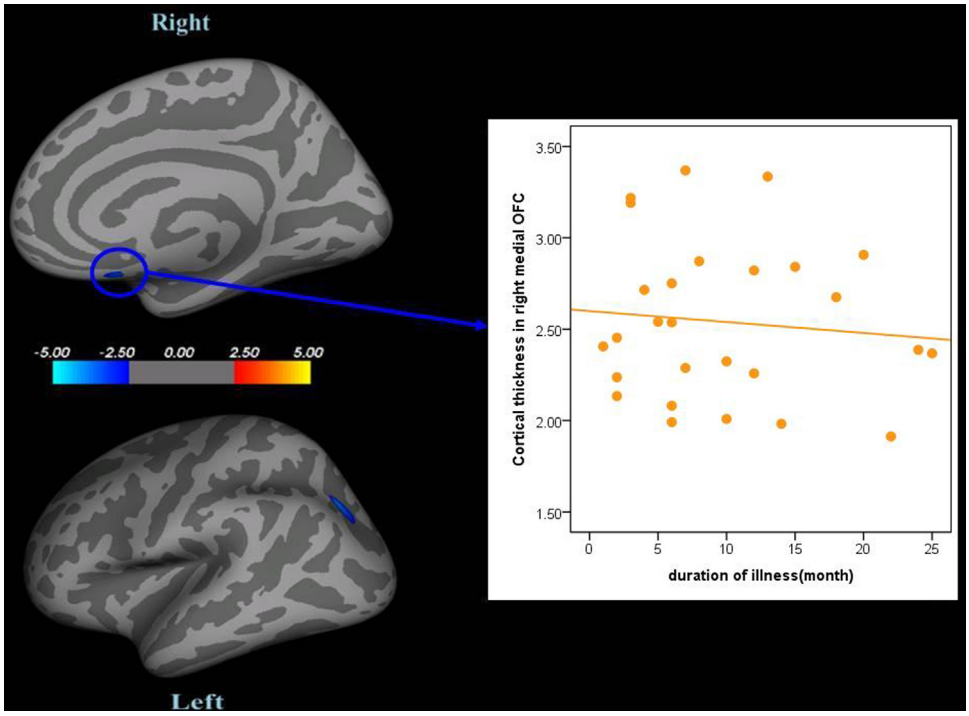

Fig. 1. Clusters with significant differences in whole brain cortical thickness comparison between MDD and HC (left). Scatter plot shows the negative correlation between course of illness with cortical thickness of the right medial OFC in MDD patients (right). Whole brain group comparisons by Qdec with threshold $p < 0.001$, uncorrected, clusters > 100 vertices, with age, gender, and ICV as covariates. Left, left hemisphere; Right, right hemisphere.

Table 3
Clusters with significant group differences on caudate-cortical thickness correlations.

Hemisphere	Annotation	−log (*p*)	Talairach			Number of vertex	Size (mm^2)
			X	*Y*	*Z*		
L	Superior parietal gyrus	4.67	−15	−54	61	354	144.13
R	Superior parietal gyrus	3.38	30	−72	−19	109	45.43

Notes: whole brain group comparisons were conducted by Qdec with threshold $p < 0.001$, uncorrected. Clusters with vertices > 100 were shown. Age, gender and ICV were taken as covariates.

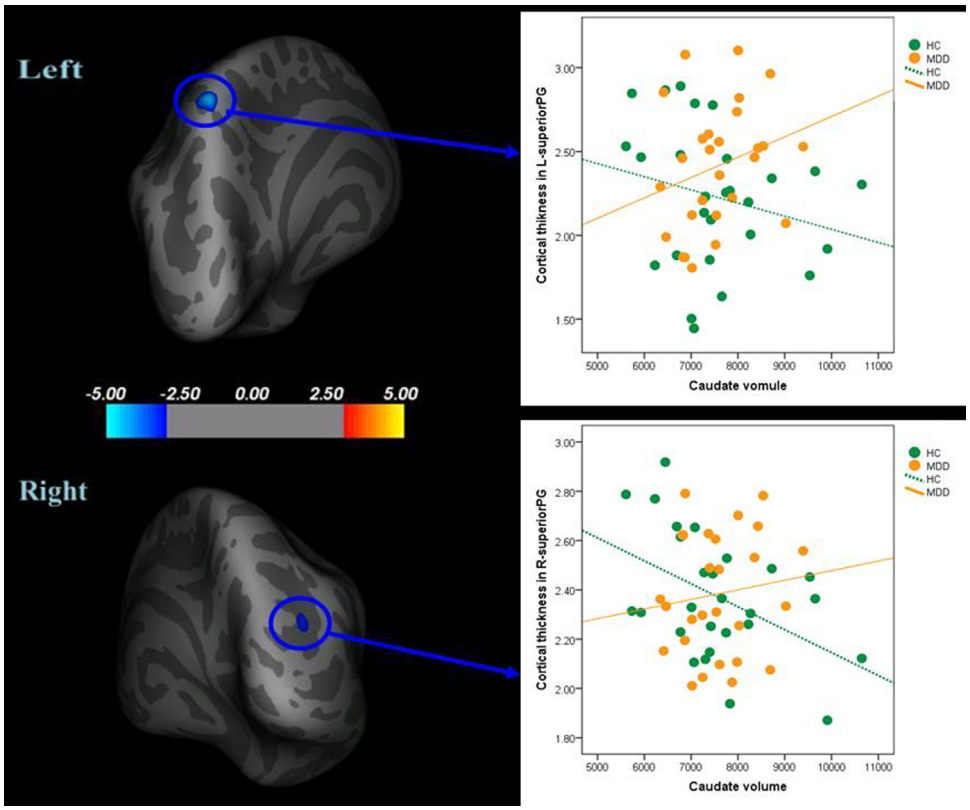

Fig. 2. Clusters with significant group differences in association between caudate volume and cortical thickness. The difference in caudate–cortical connectivity here should be interpreted as the interaction between caudate volume and group for patients with MDD and healthy controls. Scatter plots illustrate each significant cluster with the bilateral superior parietal gyrus volume on the *X*-axis and mean cortical thickness of ROI on the *Y*-axis. A positive correlation is shown in MDD patients, but healthy controls show a negative correlation. In the plots, mean thickness values and regression lines are shown in green for healthy controls and orange for the patients with MDD. $p < 0.001$, uncorrected, clusters > 100 vertices.

orbitofrontal cortex is inversely related to duration of illness, suggesting a change in cortical thickness with illness progression in MDD. Substantial evidence suggests that the medial orbitofrontal cortex mediates depressive symptoms through dense interconnections with brain structures that have putative involvement in MDD pathophysiology, such as the basal ganglia, the thalamus, the amygdala, and the hippocampus, all of which are involved in top-down neuronal modulation of emotion (Price and Drevets, 2010; Smith et al., 2013). The increased cortical thickness in the medial orbitofrontal cortex we found may reflect a compensatory mechanism to cope with less efficient self regulation due to dysfunction of the limbic structures in MDD. Indeed, recent functional studies using pleasant stimuli (images) or reward-related tasks to study MDD had reported that hyperactivation in the medial prefrontal cortex may result from compensation for hypoactivation of limbic structures including the ventral and dorsal striatum (Keedwell et al., 2005; Forbes et al., 2006; Forbes et al., 2009). However, in contrast to our finding of increased cortical thickness in the right medial orbitofrontal gyrus, van Eijndhoven et al. (2013) reported reduced thickness in the left medial orbitofrontal cortex. The discrepancy may be due to the inclusion of medicated MDD patients in their study.

The inferior parietal gyrus, another region with increased cortical thickness in our study, has not been reported in MDD patients. Although the parietal region is mainly involved in visual perception and visuomotor control, anatomically reciprocal fronto–parietal connections are also involved in emotion processing and cognitive changes with MDD (Brody et al., 2001). Previous researchers had proposed that antidepressants (citalopram) may change glucose metabolism level in the precuneus, suggesting that the parietal lobe may be involved in the neurobiological mechanisms for the occurrence of depressive symptoms (Smith et al., 2002). Another recent study by Cavanna et al. (2006) also noted that the precuneus may be involved in episodic memory and emotion information processing. In a group at high risk of depression, abnormal activation of the superior parietal lobule was reported compared with low-risk controls (Chan et al., 2008). Our findings suggest that parietal dysfunction in MDD patients may already be evident at the early stage of the illness and may not a

Table 4
Partial correlations between cortical ROIs/subcortical volumes and scale scores.

	Health group ($n=27$)					Depressed patients ($n=27$)						
	SHAPS	TEPS-ANT	TEPS-CON	TEPS	BDI	SHAPS	TEPS-ANT	TEPS-CON	TEPS	BDI	HRSD	course
L_superior PG	0.08	−0.01	−0.07	−0.05	−0.03	0.06	−0.32	0.07	−0.14	0.41*	0.29	−0.25
R_superior PG	−0.07	0.04	−0.04	0.00	−0.01	0.28	−0.38	−0.17	−0.31	0.37*	0.35	−0.16
R_medial OFC	−0.09	0.04	0.14	0.10	−0.27	0.01	0.14	0.10	0.13	−0.01	0.09	−0.45*
L_inferior PG	−0.09	0.17	0.05	0.12	0.03	0.21	0.01	0.10	0.06	0.04	0.19	0.16

Notes: BDI: Beck Depression Inventory; HRSD: The Hamilton Rating Scale for Depression; OFC: Orbito-frontal cortex; SHAPS: Snaith-Hamilton Pleasure Scale; TEPS-ANT: Temporal Experience of Pleasure Scale-Anticipatory Pleasure Subscale; TEPS-CON: Temporal Experience of Pleasure Scale-Consummatory Pleasure Subscale; PG: parietal gyrus

* : $p < 0.05$;; Age, gender and ICV were taken as covariates.

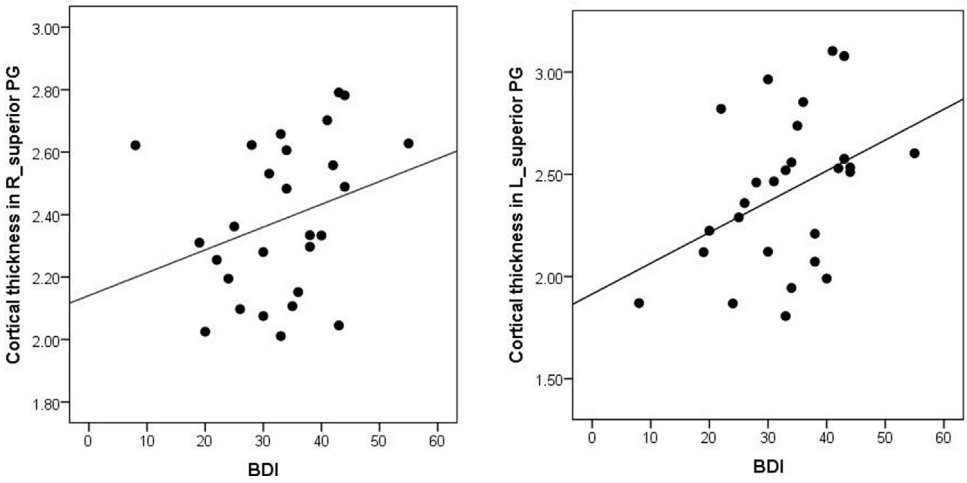

Fig. 3. Scatter plots between cortical ROIs/subcortical volumes and BDI in MDD patients, with age, gender and ICV as covariates.

result of antidepressant treatment.

Another interesting finding from the present study is the inverse correlation between the volumes of the caudate and the bilateral superior parietal gyri in MDD patients relative to controls. Only one previous study has reported correlational analysis of the pattern of cortical thickness in MDD, and they found increased correlation between prefrontal and parietal cortical thickness in first-episode MDD patients (Qiu et al., 2014). We did not find any evidence of increased connectivity between the caudate and the dorsolateral PFC as reported by Furman et al. (2011), but increased caudate–parietal lobe connectivity. Recent research on first-episode, drug-naive MDD patients found altered functional connectivity within the default mode network (DMN) (Zhu et al., 2012; Guo et al., 2013). The bilateral superior parietal lobes, as components of the DMN, may be disturbed in depression (Smith et al., 2002; Cavanna and Trimble, 2006). The caudate nucleus is functionally connected with DMN via dopaminergic projections. It is possible striatal dopamine circuits may be involved in the regulation of cognition and mood by modulating the DMN in MDD. Of note, evidence from first-episode, treatment-naive MDD patients has shown increased nodal centralities in the caudate nucleus and parietal regions (Zhang et al., 2011), and the negative correlations between depression severity and these regions suggest that the change in caudate-cortical connectivity is related to the severity of depressive episode. In sum, increased caudate-parietal connectivity suggests their roles in coordinating whole-brain networks, presumably in response to the pathological mechanism in the early course of depression.

To our knowledge, no other study has identified cortical thickness abnormalities in first episode MDD patients specifically linked to anhedonia. Contrary to our predictions, we did not find any correlation between anhedonia and subcortical volume or cortical thickness. Previous studies have reported that anhedonia is related to reduced caudate volume (Harvey et al., 2007; Pizzagalli et al., 2009). Harvey et al., 2007 found the volume of the anterior caudate to be significantly decreased as the level of trait anhedonia increased in non-clinical subjects. Pizzagalli et al. (2009) also reported MDD participants with elevated anhedonic symptoms showing reduced bilateral caudate volume. The lack of a significant relationship in our study might in part be explained by methodological and sample differences. Harvey et al. 2007 used the Chapman physical anhedonia scale (Chapman et al., 1976) to determine hedonic capacity. On the other hand, Pizzagalli et al. (2009) used the Beck Depression Inventory-II (BDI-II) (Beck et al., 1996) anhedonic subscale to measure anhedonia. Previous brain imaging studies had reported that anhedonia is correlated with activation in cortical and subcortical regions (Keedwell et al., 2005; Forbes,2009), and depression severity scores are also correlated with these regions activation. In this study, we used the TEPS, which is a more recently developed instrument capturing the anticipatory and consummatory components of pleasure experience. However, given the small sample size of our study, our findings are preliminary.

5. Limitations

This study has several limitations. First, although our findings

are consistent with other clinical studies, it should be noted that liberal thresholds were used for the analyses and the inability to correct for multiple comparisons is an issue of concern. Our findings should be considered to be preliminary and future studies with a larger sample size would be helpful to confirm our results. Secondly, subcortical volumes in our study were overestimated automatically by FreeSurfer and the results should be interpreted cautiously. Indeed, previous studies have reported reliability and statistical power analyses in different samples (Liem et al., 2015). Thirdly, this study employed a cross sectional design and could not address the question of whether the structural differences we observed close to illness onset reflect altered brain maturation that developed over time or not. Prospective studies are required to investigate the temporal course of cortical thickness changes in MDD patients. Finally, compared with the anatomical connectivity obtained by diffusion-based imaging, the method based on a correlational analysis of cortical thickness we used in the present study only measured anatomical connectivity indirectly. It is not clear whether the altered correlations represent real alterations in functional connections or simply reflected parallel effects of illness pathophysiology on different brain regions. Future studies should combine resting-state functional MRI to investigate cortical thickness with levels of glutamate and DMN activity.

6. Conclusions

In contrast to observations of volume reduction in studies of chronic patients with MDD, the present study found that first-episode, unmedicated MDD patients have increased cortical thickness in some brain regions and increased caudate–cortical connectivity patterns. These alterations may be related to the pathophysiological manifestations in the early course of depressive illness. Future longitudinal imaging studies are needed to determine whether there are dynamic changes in cortical thickness in MDD patients.

Conflicts of interest

None.

Acknowledgments

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