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Original Data

Neural correlates of severity in major depressive disorder: A combined structural and resting-state functional MRI study

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ABSTRACT

Major depressive disorder (MDD) is a disabling and severe psychiatric disorder with high risk of suicide, and adulthood is one of the most probable period for the onset. The neural basis underlying the young adults with MDD remains underexplored. In this study, we have investigated the cortical and subcortical alterations of neuroanatomical structures and functional activation in twenty-three young depressive patients with suicide attempt versus forty-five healthy controls. Significant disruptions of regional gray matter volume at left middle frontal extending to superior frontal involved with cognitive processing were found correlated with anxiety scores in MDD patients. Increased cortical thickness at right orbital frontal responsible for decision making was correlated with severity of suicide. Further, increased functional activation at left auditory association cortex was a hallmark of hallucinations in MDD, which was directly associated with depression severity. Moreover, decreased spontaneous brain activity at right inferior frontal was also found, reflecting lower inhibition control in MDD patients. The abnormal structural and functional findings at fronto-cortical areas implied the dysfunctional cognitive control and emotion regulation in MDD. The alterations correlated with clinical scores might indicate the reliable neural markers for MDD.

1. Introduction

Major depressive disorder (MDD) is a chronic and debilitating neuropsychiatric disorder with lifetime prevalence rates estimated at 15–18 %, and adulthood is one of the most probable period for the onset of the first episode of major depression (Malhi and Mann, 2018). MDD is characterized by persistent and pervasive feelings of sadness, guilt and worthlessness, and together with anxiety disorders remained among the leading cause of burden worldwide with prevalence estimates and disability weights comparatively higher than many other disease (Collaborators, 2022). MDD patients have a high risk of suicide, and suicide is also the fourth leading cause of mortality in young people (Organization, 2021). Thus, with a high incidence rate, MDD has caused heavy social and economical burden. While the underlying neurobiology mechanisms are still under-explored. Neuroimaging technique such as magnetic resonance imaging (MRI) has provided a non-invasive way to gain insight into the brain anatomical structures and neuronal functional activity. Yet, there are still limited studies specifically on young adults with MDD and suicide attempt.

Structural MRI offers an effective way to investigate the neuroanatomical structures, and the volumetric analyses of gray matter (GM) and surface calculation of cortical thickness (CT) were two main methods used. MDD patients with suicide attempt have been reported to have significantly decreased GM volume in fronto-striatal-limbic network (Wagner et al., 2011), and parietal cortex compared to controls (Lee et al., 2016). Inconsistently, the other study has reported greater GM volume at prefrontal brain regions in adult MDD patients with the high lethality suicide attempt (Rizk et al., 2019). Disruptions of CT in MDD patients have been found at frontal, temporal and parietal brain regions according to previous studies (Peng et al., 2015; Lener et al., 2016; Suh et al., 2019). The thickening CT at frontal brain regions of right hemisphere has been reported in first-episode and untreated mid-life MDD patients (Qiu et al., 2014). Still, inconsistent findings of lower CT in fronto-cingulate as well as temporal brain regions were reported in MDD

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with high risk for suicide (Wagner et al., 2012).

Resting state functional MRI(rs-fMRI) is also a branch of technique widely used to evaluate the brain functional activation. There are several rs-fMRI metrics used to reflect the brain functional activity such as Amplitude of low frequency fluctuation (ALFF), and Regional homogeneity (ReHo). ALFF could reflect the intensity of regional spontaneous neuronal activity (Zang et al., 2007), while ReHo is an indicator of complexity and synchronicity of the neuronal activation (Zang et al., 2004). Whole-brain ALFF analysis in depression studies has found alterations at fronto-temporo-parietal areas related to the dysfunction of affective and cognitive processes (Wang et al., 2012; Tadayonnejad et al., 2015; Zhang et al., 2016). The study has pointed out reversal alterations could exist in early and late-onset depressed patients (Guo et al., 2013). Yet, there were still limited study carried out to exam the cortical functional activation in depression.

Therefore, the primary goal of the present study was to comprehensively clarify the neural basis of young depressed patients with suicide attempt through the combination of structural and functional analyses. Firstly, we utilized voxel-based morphometry (VBM) to examine the regional structure of GM volume in adult patients with MDD in comparison with healthy controls. Secondly, we used the surface-based morphometry (SBM) to examine the CT in MDD patients compared with healthy controls. Thirdly, we also investigated the subcortical ALFF and ReHo as measurements of functional activity in MDD patients compared to controls. Finally, we calculated the surface ALFF and ReHo measurements and compared between patients and control groups. Here, we hypothesized that there will be neuroanatomical and functional alterations at cortico-subcortical brain regions in MDD compared to controls. Further, we expected those brain morphometry characteristics to be correlated with the severity of clinical scores.

2. Methods

2.1. Participants

Fifty-three young depressed adults were recruited from the Department of Psychiatry at the First Affiliated Hospital of Chongqing Medical University, China. This work was carried out in accordance to the Declaration of Helsinki, and the study was approved by the research ethics committee of the university. All participants' informed consent was obtained after the procedures explained. Inclusion criteria for MDD and control groups involved the following: right-handed (determined by patient interview and parents confirmation), age between 15 and 29 years and having normal to corrected vision. The Structured Clinical Interview for Diagnostic and Statistical Manual IV (DSM-IV) Axis I disorder (SCID-I) was administered for the diagnosis of depressive disorder by two qualified psychiatrists. Exclusion criteria included psychiatric axis-I co-morbidity, a history of neurological diseases or seizures, significant head injury or concussion, standard MRI contraindications, history of substance/alcohol abuse or dependence, history of psychiatric disorders or suicide among first-degree relatives, and other clinically relevant abnormalities based on medical history or laboratory examination.

The severity of depression was measured at the day of MRI scan using the 17-item Hamilton Depression Scale (HAMD-17) and Beck Depression Inventory (BDI). And the anxiety was measured using the Hamilton Anxiety Scale (HAMA). The Beck Hopelessness Scale (BHS) and Scale for Suicide Ideation (SSI) were also administered to patients to assess the severity of hopelessness and suicidal ideation. The history of suicide attempt, including the number of suicide attempts, the methods used and the time since last attempt was confirmed. The trait impulsivity was assessed using Barratt Impulsiveness Scale 11th version (BIS-11).

Additionally, forty-seven right-handed healthy controls (HC) matched for gender, age and education, were recruited from the local community through advertisements. The subjects were screened with the Structured Clinical Interview for DSM-IV, non-patient edition (SCID-NP). Subjects with past or current DSM-IV axis-I diagnosis, neurological illness, history of head trauma with loss of consciousness, and history of psychiatric disorders or suicidal behavior among first-degree relatives were excluded.

2.2. Imaging protocols

All MR images were acquired with 3.0-T GE Signa HDxt (General Electric Healthcare, Chicago, Illinois, USA) scanner equipped with a standard 8-channel head coil. Contiguous sagittal T1-weighted images across the entire brain were acquired with a fast gradient echo (FGRE) sequence: time of echo (TE) = 3.3 msc, time of repetition (TR) = 8.3 msc, flip angle = 12°, field of view (FOV) = 240 mm, voxel size = 0.469 × 0.469 × 1 mm^3, no gap.

The rs-fMRI data were obtained using an echo-planar image (EPI) pulse sequence with the following parameters: 33 axial slices, TE = 40 msc, TR = 2000 msc, in-plane resolution = 64 × 64 pixels, flip angle = 90°, FOV = 240 mm, voxel size = 3.75 × 3.75 × 4 mm^3, no gap.A total of 240 time points was obtained over 8 min.

2.3. Data processing and analysis

2.3.1. Anatomical image processing

Both anatomical and functional image processing was conducted using DPABISurf, a toolbox offering an user-friendly interface for brain imaging data processing and analysis (Yan et al., 2021). The toolbox was executed in MATLAB (R2021b). For processing and analysis-steps, default parameters in accordance with standard protocol were used. The images were resampled to the original size (i.e., 0.469 × 0.469 × 1 mm^3 for an anatomical image; 3.75 × 3.75 × 4 mm^3 for a functional image). The T1-weighted (T1w) image was corrected for intensity non-uniformity, and used as T1w-reference throughout the workflow. The T1w-reference was then skull-stripped. Further, Brain tissue segmentation of cerebrospinal fluid (CSF), white-matter (WM) and GM was performed on the brain-extracted T1w.

Brain surfaces were reconstructed using *recon-all* (FreeSurfer 6.0.1) (Dale et al., 1999), and the brain mask estimated previously was refined with a custom variation of the method to reconcile the derived segmentations of the cortical GM. Volume-based spatial normalization to one standard space (MNI152NLin2009cAsym) was performed through nonlinear registration.

After the anatomical image preprocessed, the volumetric GM and surface CT was smoothed using a Gaussian filter with 6-mm full width at half maximum (FWHM).

2.3.2. Functional image processing

For each of the resting-state (rs) blood-oxygenation-level dependent (BOLD) signal per subject, the following preprocessing was performed. The first 10 volumes were removed, and then, a reference volume and its skull-stripped version were generated. The BOLD reference was then co-registered to the T1w reference. Head-motion parameters with respect to the BOLD reference are estimated. BOLD runs were slice-time corrected. The BOLD time-series were then resampled to surface space (*fsaverage5*) and original volumetric space. Principal components are estimated after high-pass filtering the *preprocessed BOLD* time-series for the two component-based noise correction (*CompCor)* variants: temporal (tCompCor) and anatomical (aCompCor). tCompCor components are then calculated from the top 5 % variable voxels within a mask covering the subcortical regions. This subcortical mask is obtained by heavily eroding the brain mask, which ensures it does not include cortical GM regions. For aCompCor, components are calculated within the intersection of the aforementioned mask and the union of CSF and WM masks calculated in T1w space, after their projection to the native space of each functional run.

After the functional images preprocessed, covariates nuisance was

further regressed to acquire the subcortical ALFF/ReHo at volumetric space and cortical ALFF/ReHo at surface space. ALFF corresponds to the mean amplitude low-frequency fluctuation bands (0.01–0.1 Hz), and ReHo represents the homogeneity of a time course for a given voxel relative to that of the time courses of the 26 nearest neighboring voxels. Finally,those two metrics were smoothed through a Gaussian filter with 6-mm FWHM.

2.4. Statistical analysis

Differences in those anatomical and rs-fMRI metrics between MDD patients and controls were assessed using Statistical Analysis in DPABISurf. In order to investigate GM volumetric changes in depressive patients, a two-sample t-test was used. Age, gender and total intracranial volume were entered into the general linear model as covariates. An initial voxel-wise threshold was set at $p < 0.001$ with subsequent family-wise error (FWE) corrected p-value < 0.05 at cluster level. Also, differences in CT between groups were assessed with age and gender entered into the general linear model as covariates. An initial voxel-wise threshold was set at $p < 0.001$. A threshold-free cluster enhancement (TFCE) approach was used to correct for multiple comparisons, and a significance threshold of $q < 0.025$ was used for each hemisphere.

Two-sample t-tests were also conducted to investigate the measurements of volumetric and cortical ALFF/ReHo between depression and control groups. Together with the age and gender, the generated mean FD_Jenkinson value was included as covariance to control the head motion effects. An initial voxel-wise threshold was set at $p < 0.05$, and with subsequent FWE corrected p-value < 0.05 at cluster level for volumetric analyses. While for surface analysis, an initial voxel-wise threshold was set at $p < 0.05$. Still, a TFCE approach was used to correct for multiple comparisons, and a significance threshold of $q < 0.025$ was used for each hemisphere.

Further, we extracted the mean value of GM volume, CT and ALFF of the significant clusters in both MDD and controls, and post-hoc two-sample t-tests were carried out to compare the group differences. Also, correlation analyses were carried to examine relationship between those structural and functional measurements and clinical scores.

3. Results

3.1. Participants and clinical characteristics

Fifty-three MDD patients and forty-seven healthy controls were initially screened for inclusion in the study. Thirty MDD patients and two healthy controls were excluded for missing and invalid imaging (head motion larger than 3 mm translation or 3° rotation), or demographics data, leaving twenty-three MDD patients (16 females/7 males, 20 medicated/3 non-medicated, 21.78 ± 3.66 years old) and forty-five healthy controls (29 female/16 males, 20.56 ± 1.88 years old) included into the analysis. The demographic and clinical characteristics of these individuals are shown in Table 1.

Table 1
Demographic and clinical characteristics of participants.

Measure (mean, S.D.)	MDD (n = 23)	HC (n = 45)	Statistics
Gender, n			
Female	16	29	[a] p = 0.673
Male	7	16	
Age, yrs	21.78(3.66)	20.56(1.88)	t = 1.84, p = 0.071
Education, yrs	13.52(1.68)	13.56(1.55)	t = 0.083, p = 0.93
HAMA	16.91(6.25)	4.51(3.11)	t = 10.97, p < 0.0001
HAMD-17	21.30(8.60)	3.82(2.32)	t = 12.84, p < 0.0001
BDI	25.50(7.75)	3.80(3.31)	t = 16.11, p < 0.0001
BIS-11	75.05(9.79)	61.42(8.29)	t = 5.95, p < 0.0001
BHS	10.68(4.22)	3.78(2.45)	t = 8.47, p < 0.0001
SSI	11.14(5.24)	2.89(2.30)	t = 8.99, p < 0.0001
Suicide history	2.47(2.21)	-	-
Medication, n		-	
Medication free	3(21.7 %)	-	
Mood stabilizers	2(8.7 %)		
Antidepressants	15(65.2 %)	-	
Anti-psychotics	3(13 %)		

*Note: HAMA – Hamilton Anxiety Scale; HAMD – Hamilton Depression Scale. BDI – Beck Depression Inventory; BIS - Barratt Impulsiveness Scale 11th version; BHS – Beck Hopelessness Scale; SSI – Scale for Suicide Ideation.
[a] Indicates p value for Chi-square test.

3.2. Group comparison of GM volume

Significant differences were observed in regional GM volume between depression and control groups. MDD patients showed a significantly decreased GM volume in the left middle frontal gyrus (MFG) extending to superior frontal gyrus (SFG) (Peak value t = 5.33; at [− 33, 48, 27]; k = 1500 voxels) at $p < 0.001$ (corrected) at cluster level (see Fig. 1 & Table 2).

3.3. Group comparison of cortical thickness

Significant differences were observed in regional CT between depression and control groups. MDD patients showed a significantly increased CT in the right orbital frontal cortex (OFC; peak value t = 5.31; at [− 18, 62, − 52]; k = 329 vertices) at $p < 0.001$ (corrected) at cluster level (see Fig. 2 & Table 2).

3.4. Group comparison of ALFF measurement of functional activity

Significant differences were observed in regional cortical ALFF measurement between depression and control groups. MDD patients showed a significantly increased ALFF in the left auditory association cortex (Peak value t = 4.03; at [− 49, − 43, 4]; k = 174 vertices) at $p < 0.05$ (corrected) at cluster level (see Fig. 3***(a)*** & Table 2). Meanwhile, MDD patients had a significantly decreased ALFF at the right inferior frontal cortex (IFG, peak value t = − 3.65; at [39, 31, 31]; k = 133 vertices) at $p < 0.05$ (corrected) at cluster level (see Fig. 3***(b)*** & Table 2).

3.5. Group comparison of ReHo measurement of functional activity

No significant differences were found in regional ReHo measurement between the depression and control groups under both volumetric and surface space.

3.6. Group comparison of signal from region of interests and association with clinical scores

The post-hoc analyses showed that mean GM volume in the left MFG were significantly lower in MDD (0.461 ± 0.049) patients compared to controls (0.529 ± 0.048), and positively correlated with HAMA scores (r = 0.451, p = 0.035) (see Fig. 4***(a)***). The mean CT at the right OFC was significantly higher in MDD group (2.485 ± 0.309) compared to controls (2.173 ± 0.189), and it was negatively correlated with SSI scores (r = − 0.48, p = 0.032) (see Fig. 4***(b)***). Further, the mean ALFF at left auditory association cortex was significantly higher in MDD patients (0.363 ± 0.350) compared to controls (0.053 ± 0.221), and it was also found positively correlated with BDI scores (r = 0.423, p = 0.0499) (see Fig. 4***(c)***). Whereas the mean ALFF at right IFG was found lower in MDD group (0.239 ± 0.220) compared to controls (0.551 ± 0.295), and no significant correlation was found with the clinical scores (see Fig. 4***(d)***).

4. Discussion

The present study examined the morphometric structures including regional GM volume and CT, and also measured the spontaneous brain functional activity through ALFF and ReHo in young MDD patients.

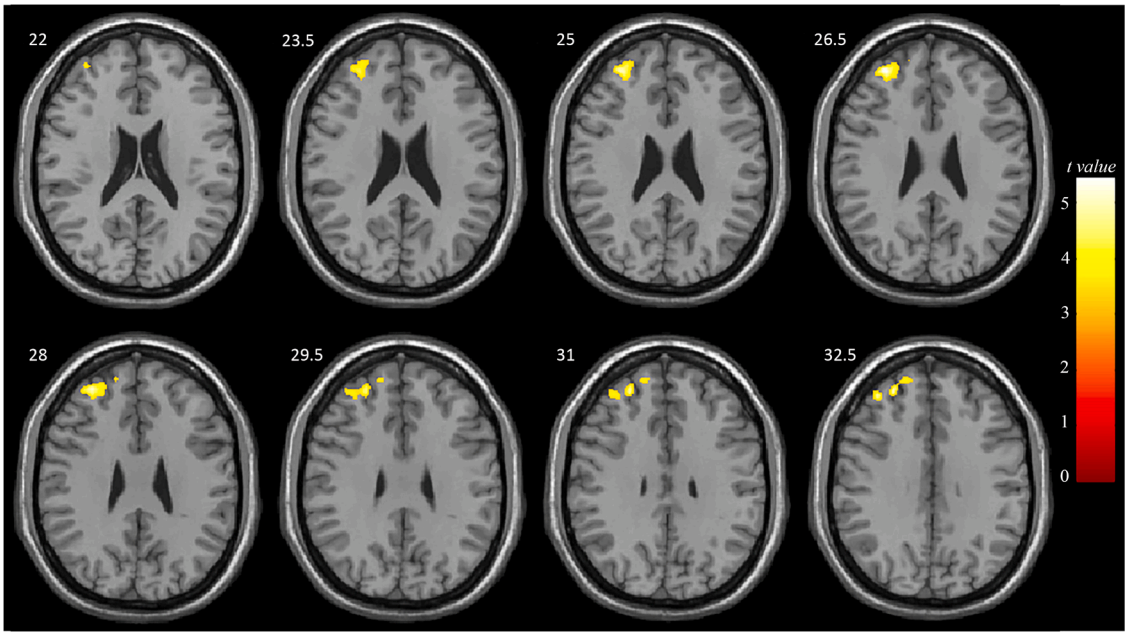


Fig. 1. MDD patients showed a significantly decreased GM volume at left middle frontal extending to superior frontal cortices. The color bar depicts the t-statistics.

Table 2
Locations of regional differences in GM volume, CT value and ALFF.

Region	MNI coordinates of peak			Peak t-value	Spatial extent (in contiguous voxels/ vertices)
	x	y	z		
GM volume					
MDD < HC					
L. MFG	-33	48	27	5.33	1500
L. SFG	-20	54	34	4.05	304
CT					
MDD > HC					
R. OFC	-18	62	-52	5.31	329
ALFF					
MDD > HC					
L. Auditory association cortex	-49	-43	4	4.03	174
MDD < HC					
R. IFG	39	31	31	-3.65	133

*Note: L. – left; R. – right. MFG – Middle frontal gyrus; OFC – Orbital frontal cortex; IFG – Inferior frontal gyrus.

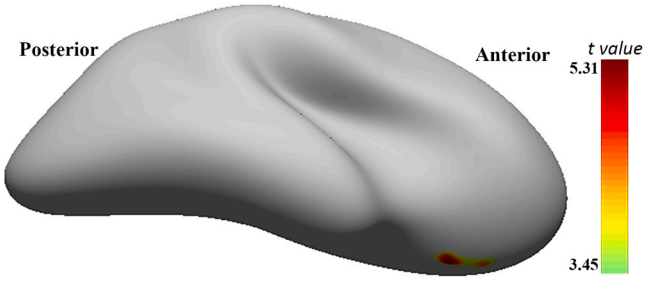


Fig. 2. MDD patients showed a significantly increased CT value at right orbital frontal cortices. The color bar depicts the t-statistics.

Firstly, we found decreased GM volume in the left MFG extending to SFG in MDD patients compared to the healthy controls. Further, greater CT at the right OFC was found in MDD patients; Moreover, the ALFF measurements of functional activation were found increased at left auditory association cortex whereas decreased at right IFG in MDD patients compared to controls. Further, analyses across those altered structural and functional features showed that decreased GM volume was positively correlated with HAMA scores, and greater CT was negatively correlated with severity of suicide attempt in MDD patients. Additionally, the increased functional activity at left auditory association cortex was positively correlated with BDI scores for depression.

The decreased GM volume at MFG and SFG has been reported in previous studies on first-episode, medication-naive MDD patients (Qiu et al., 2014; Peng et al., 2016; Yang et al., 2015). The volumetric differences of left MFG were found to be predictive of individual differences in cognitive control capacity (Eayrs and Lavie, 2019), thus, suggesting its role in cognition processes. In line with the structural alteration, the depressive patients were found to have significantly lower response to reward stimulus in the MFG (Oh et al., 2021). The left SFG has been suggested functionally coupled with auditory cortices and involved with the cognitive reappraisal process to increase emotional response (Korb et al., 2015). We have also found the reduction of GM volume positively correlated with the anxiety scores. The reason of this correlation was that left SFG also a key region in the anxious-specific pathway for self-control regulation according to a very recent study (Zhang et al., 2022). The deficits of GM volume in MDD patients implied the dysfunctional cognitive and emotional control.

Consistent with our findings, previous studies have reported increased CT at OFC (Qiu et al., 2014). The OFC is involved in executive functions, and plays an important role in decision making (Antoine Bechara et al., 2000). Asymmetric brain functions in the subregions of dorsolateral prefrontal cortex (DLPFC) including MFG and SFG existed for emotional processing were reported (Herrington et al., 2010), Specifically, the MFG showed more activation in the context of pleasant but not unpleasant words. Moreover, this area showed less activity in the context of unpleasant than neutral words.Thus, the MFG functions deferentially across valence spectrum - up-regulated for pleasant emotional stimuli and down-regulated for unpleasant emotional stimuli. Moreover, in this study, abnormal DLPFC asymmetries for emotional processing were found with depression symptoms. Similarly, we have also previously reported the existence of abnormal coupling of biochemical and functional connection in the left subcortical structure of depressive patients (Tang et al., 2018). The GM loss we found could well-explain the abnormal asymmetries. Furthermore, the left DLPFC

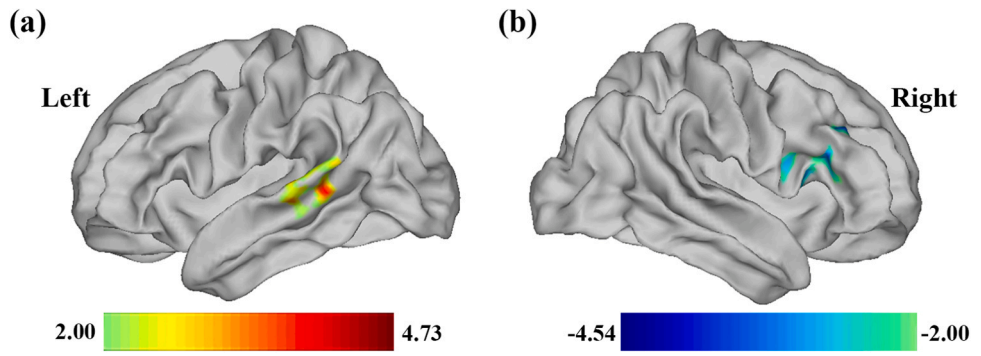


Fig. 3. MDD patients showed significantly altered functional activity. (a) increased ALFF measurement at left auditory association cortex; (b) decreased ALFF value at the right inferior frontal cortex.The color bar depicts the t-statistics.

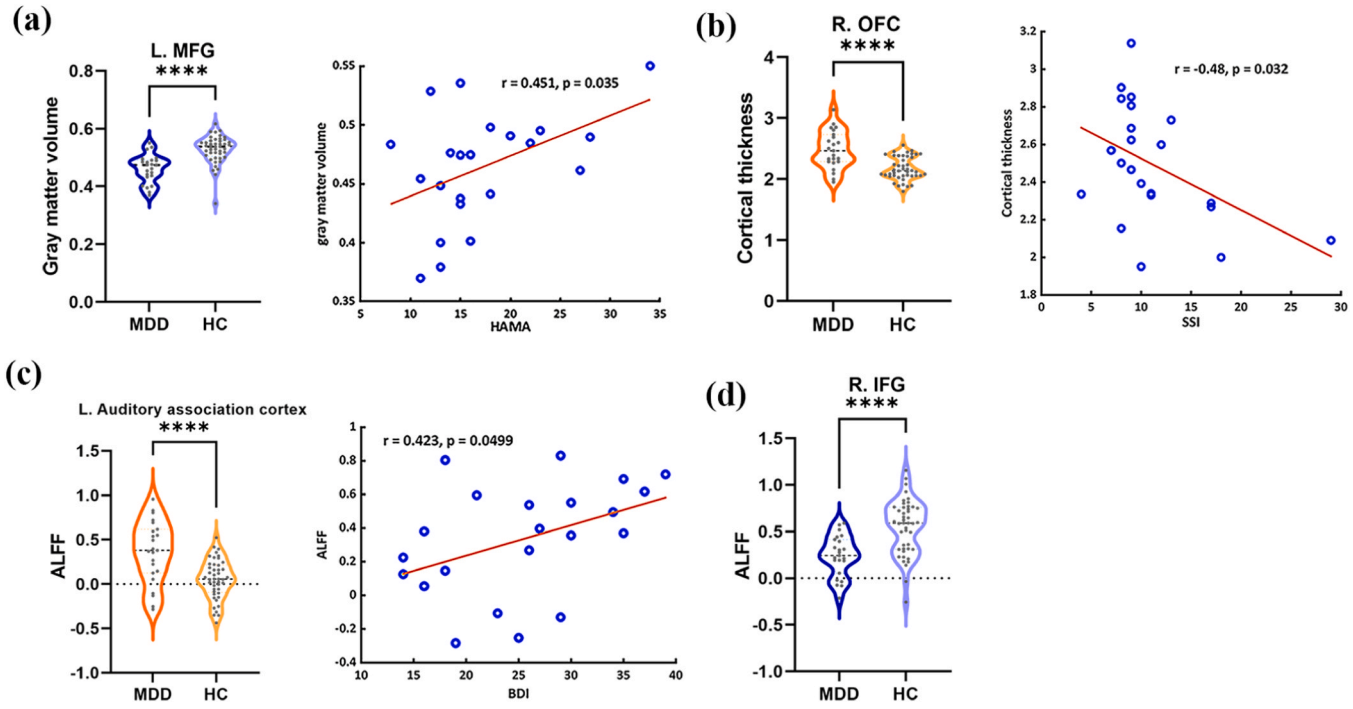


Fig. 4. The post-hoc analyses of mean signal at significant brain areas, and the measurements correlation with clinical scores. (a) The significantly decreased GM volume at left MFG in MDD patients was found correlated with HAMA scores ($r = 0.451$, $p = 0.035$). (b) The significantly higher CT at right OFC in MDD patients was found correlated with SSI scores ($r = -0.48$, $p = 0.032$). (c) The significantly higher ALFF value at left auditory association cortex was correlated with BDI scores ($r = 0.423$, $p = 0.0499$). (d) The significantly lower ALFF at right IFG in MDD patients showed no correlation with clinical scores.

and right OFC and their respective central-executive network (CEN) and default mode network (DMN) was suggested to significantly contribute to risk-taking behavior and risky decision-making (Nejati et al., 2018). This could explain the increased CT at right OFC correlated with the severity of suicide scores found in our study.

The increased functional activation indicated by ALFF was found at the left auditory association cortex. This area is located at the superior temporal, and the same location has been found to be activated by nonverbal/abstract auditory stimuli (Frey et al., 2004). Auditory hallucinations perceptions of voices in the absence of external stimuli commonly occur in psychotic disorder. Auditory hallucinations associated with activation at superior cortex were reported, which involved with sensory processing (Shergill et al., 2001). Moreover, we have found the abnormal activation was correlated with severity of depression in MDD patients. Auditory hallucinations occur in depressed adults with a six percent, and the presence could be linked with more psychopathology profile including severe course and increased risk of hospitalization (Waters, 2010). The findings suggest that abnormality in brain activity at auditory association cortex could be a critical neural biomarker for auditory hallucinations in depressed patients.

Another major finding related to changes in ALFF measurement is at right IFG. This region, especially the right side is considered to play an important role in core cognitive-control related processes such as inhibitory control, attention allocation and decision making (Aron et al., 2004; Or-Borichev et al., 2022). The previous study has reported its role in reappraising social emotions (Grecucci et al., 2013). Further, transcranial direct current stimulation (tDCS) over the specific right IFG attenuated the psychophysiological response to the unpredictable threat in healthy subject, thus offering a more direct way to demonstrate its role in emotional regulation (Herrmann et al., 2018). The IFG was suggested having highly functional connections with the aforementioned auditory association cortex (Yeo et al., 2011). The found decreased functional activity here might suggest dysfunctional inhibitory and emotion modulation in MDD patients.

There were some limitations in the current study. Firstly, most of our patients were on medication due to practical and ethical issues, thus

possible confounding effects of medication could not be ruled out. Secondly, women are about twice as likely as men to develop depression, and may have different clinical symptoms (Kuehner, 2017). Therefore, future study with a large number of samples could be carried out to examine the alterations in women and men, respectively.

In conclusion, this study examined the structural and functional alterations in young adults with MDD. The disruptions of GM structures at left MFG extending to SFG implied the dysfunctional executive functions, thus driving the anxiety in MDD patients. Further, the abnormal CT at right OFC, together with disrupted frontal structures, resulted in dysfunction in exerting control over risky decision making, and generated the inappropriate decisions of suicide behaviour in MDD patients. Moreover, the abnormal functional activity at right auditory association cortex reflected the presence of auditory hallucinations, which was the prominent psychotic feature in depressive patients. Lastly, the decreased neuronal activity found in right IFG implied the dysfunctional inhibition control and emotional modulation in MDD patients. Altogether, the structural and functional alterations found in this study could help elaborate the underlying neural mechanism of the psychiatric depressive disorder.

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CRediT authorship contribution statement

Zhang XL: Conceptualization, Formal analysis, Funding acquisition, Visualization, Writing – original draft. **Cao J:** Data curation, Funding acquisition, Writing – review & editing. **Chen XR & Huang Q:** Formal analysis; **Hong S, Chen JM, Ai M, Gan Y & He JL:** Resources. **Kuang L:** Project administration, Funding acquisition, Writing – review & editing. **All the authors:** Approval of the final submission.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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