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Anomalous functional connectivity within the default-mode network in treatment-naive patients possessing first-episode major depressive disorder

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Abstract

Background and Objective: Previous studies have shown that the default-mode network (DMN) has a substantial role in patients with major depressive disorder (MDD). However, there is a shortage of information regarding variations in the functional connectivity (FC) of the DMN of treatment-naive patients with first-episode MDD. The present study aims to explore the FC of the DMN in such patients.

Methods: The study population consisted of 33 patients and 35 controls, paired regarding age, gender, education level, and health condition. Depression severity was assessed through the Hamilton Depression Scale (HAM-D), and subjects underwent evaluation during the resting-state through functional magnetic resonance imaging (rs-fMRI). To assess the result, we used FC and ICA. We used Spearman's correlation test to detect potential correlations between anomalous FC and severity of HAM-D scores.

Results: We have found a decreased FC in the left medial orbitofrontal gyrus (MOFG) and right marginal gyrus (SMG) in depressive patients compared to controls. There was a negative correlation between abnormal FC in the right SMG and HAM-D scores. We have not found any increase in FC of the DMN in treatment-naive, first-episode of MDD patients.

Conclusions: Our study provided evidence of a negative correlation between abnormal FC in the DMN and severity of depression symptoms measured by HAM-D in treatment-naive MDD patients. This finding could shed some light on the relevance of DMN for understanding the pathophysiology of cognitive impairment in MDD.

Abbreviations: DMN = default-mode network, FC = functional connectivity, ICA = independent component analysis, MDD = major depressive disorder, MOFG = middle orbitofrontal gyrus, PCC = posterior cingulate cortex, SMG = superior marginal gyrus.

Keywords: default-mode network, first-episode of depression, functional connectivity, major depressive disorder, resting-state functional magnetic resonance imaging

1. Introduction

Major depressive disorder (MDD) is found as a brain functional illness caused by the prevalent cognitive function deficiencies, particularly deficits that are characterized by executive functioning and temporal deficits which are indicated by memory, such as executive function, attention, and memory.[1–3] Depressive disorder and vegetative symptoms may be caused by cognitive dysfunction.[4,5] Over 300 million people have depression at all ages worldwide. Depression is a globally prominent cause for disability and has a key share in the total disease burden. The social impact of MDD may be devastating.

The treatment of this disabling condition has been successfully performed using modern antidepressant drugs such as agomelatine which is of particular interest due to a specific mechanism of action. The clinical efficacy, safety and tolerability of this compound has been widely confirmed. Agomelatine also enhances neuroplasticity mechanisms and adult neurogenesis in brain areas such as hippocampus and prefrontal cortex.[6] In addition, the role and efficacy of inhibitors of both norepinephrine and serotonin transporters (SNRIs) in major depression is well known. In particular, duloxetine has good evidence of efficacy in acute, adult MDD. The impression that duloxetine is

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an effective antidepressant in comparison with placebo, and similarly effective as various SSRIs has been confirmed.[7]

Current evidence suggests a brain network dysfunction in patients with MDD, and also that the frontolimbic network plays an essential role in the neurobiology of depression.[8–12] The default-mode network (DMN), a network which was determined as a series of areas harmonized in activity within mind-wandering, passive background thoughts, or rest.[13] It denotes for a group of brain areas mainly active in the relaxing state, known as the posterior cingulate cortex (PCC), medial prefrontal cortex, ventral anterior cingulate cortex, precuneus, inferior parietal lobule, lateral parietal cortex, medial parietal cortex, and extended lateral temporal gyrus.[12,14–16] To our knowledge, until now, there was no scientific indication of any abnormal functional connectivity occurring in the DMN in patients with MDD.[9,17] However, the results of various researchers remain inconsistent, ever conflicting. For instance, by some researchers, it was found that the incremented DMN connectivity in drug-naive MDD at rest.[12,18,19] In another study, it was demonstrated the decreased negative BOLD responses in the DMN within MDD.[20–22] Even some researchers found both incremented and reduced functional connectivity in the DMN within MDD.[23,24] These inconsistencies may be caused by some characteristics:

1. Alterations in analytical method and limited specimen sizes can considerably influence the findings;
2. drugs treatment could disturb the functional activity of the brain;
3. physio-therapeutic plays the role in the DMN abnormalities.

Antidepressants, for instance, can influence the functional connectivity in the DMN.[23] Moreover, through the transcranial magnetic stimulation, the functional connectivity in the DMN was also altered.[25–28] Via a meta-analysis and systematic review, it was found that electroconvulsive therapy could be related to the depression.[29] Consequently, our investigation on first-episode treatment-naive people with MDD may yield the benefit of reducing these confoundings.

Functional connectivity (FC), a recently offered technique, determines the relation between 2 variousor remote brain sectors reflecting these brain functional connectivity nature. Based on the former FC results of the DMN abnormalities in depression,[14,22] we assumed that in first-episode treatment-naive MDD abnormal FC would be discovered, in comparison to the controls. We also anticipate that DMN's abnormal FC could be a potential biomarker for depressions.

2. Materials and methods

2.1. Ethics declaration

All the subjects had signed a written informed consent before participating in this study. The investigation was approved by the Medical Ethics Committee of the First Affiliated Hospital of Chongqing Medical University in accordance with the Helsinki's Declaration.

2.2. Materials

The patients and controls were recruited at the Department of Psychiatry of the First Affiliated Hospital of Chongqing Medical University. The inclusion criteria for the patients included depression diagnosis by independent evaluations from 2 psychiatrists,[30] age over 18 years old, no previous or current treatment with antidepressant medication, transcranial magnetic stimulation, or electroconvulsive therapy. We used the 17-item depression scale (HAMD-17)r assessing depression severity, since it is a validated tool extensively applied in clinical practice and research.[31] The patients possessed the total scores of 24 or over it in the HAMD-17 on the MRI assessment day. The exclusion criteria include being left-handed; the neurological disorders history in the family; intense physical diseases and drug misuse; pregnancy; results of abnormal cerebral structures followed by the early MRI scanning, and the existence of other psychiatric disorder, like personality disorders or schizophrenia and associated disorders. The inclusion criteria for healthy controls included the age over 18 years, lack of any psychiatric diagnosis. Furthermore, 33 patients were included in the study and 35 people were coordinated in terms of gender, age, educational status with the same exclusion standards as depressive patients.

2.3. Resting-state functional magnetic resonance imaging (rs-fMRI)

In order to obtain the rs-fMRI, we utilized a 3.0 Tesla MRI system (GE Signa HDx) at the First Affiliated Hospital of Chongqing Medical University.

Patients and controls were asked to close their eyes and keep their heads still during the whole MRI procedure and try to stay awake. For minimizing the head movement, we utilized a quadrature birdcage head coil lined with foam. The functional imaging applied the following EPI parameters: repetition time: 2000 ms, flip angle of 90°, echo time of 40 ms, a matrix of 64×64, a field of view of 240 mm × 240 mm, number of slices of 33 axial slices, and slice thickness of 4 mm. The settings used to obtain the 3D T1-weighted anatomical images were: repetition time of 8.4 ms, flip angle of 12°, echo time of 3.3 ms, a field of view of 24 cm × 24 cm, a matrix of 256, a field of view of 24 cm slices, 33 axial slices, 156 axial slices, and slice thickness of 1 mm.

2.4. Preprocessing of data

The data associated with rs-fMRI was analyzed with Matlab, preconditioning the data imaging from the rs-fMRI was performed. Then, the first 5 time points were discarded. No contributors included the maximal displacement over 2 mm in x, y, or z-axis and over 2 of maximal rotation. The arrangement for each patient was recorded in its functional image, and a pattern was established to normalize the patients' structures (defined accordingly to the MNI's standard template), the standardization procedure of the modulation spatial deformation and the structure of the voxel size utilizing 1 mm × 1 mm × 1 mm. Ultimately, each patient's conversion matrix function structure was also normalized to the MNI space. As part of the procedure for normalizing the functional image, the head motion parameters and cerebrospinal fluid signal were considered as elimination covariates. A voxel size of 3 mm × 3 mm × 3 mm was deemed as the functional covariate. Numerous false covariates were eliminated, such as the signal from an area arranged, 6 head motion factors found by rigid body correction, and the signal from a ventricular (ROI). Objects into and distorted resting-state connectivity patterns may be induced by global signal elimination. Therefore, the global signal was preserved in the light since it could promote distortion due to the regression of the global signal.[32–34]

Table 1

Demographic characteristics of the participants.

Demographic data	patients (n = 33)	NC (n = 35)	T (or x^2)	*P* value
Gender (male/female)	33 (15/18)	35 (20/15)	0.18	.44*
Age (yr)	21.67 ± 2.07	21.80 ± 3.90	0.18	.86†
Yr of education (yr)	11.06 ± 2.01	12.08 ± 2.19	3.45	.27†
HAMD score	25.08 ± 4.16			

* The *P* value for gender distribution was obtained by Chi-Squared test.
† The *P* value were obtained by 2 sample *t*-tests.
HAM-D = hamilton depression scale, NC = normal control.

2.5. Default-mode network identification

Using the group independent component analysis (ICA) utility, ICA was carried out to eliminate the DMN components in the templates. For ICA analysis, 3 processes from the GIFT toolbox were used: separating the independent elements, data reduction, and back recreation. Considering each component, a threshold and a statistical map were set by the voxel-wise one-sample *t*-test. According to the theory of Gaussian random field, a *P* value of less than .01 shows a considerable statistical difference between the multiple comparisons. Through voxel significance, the needs are met at $P < .01$, and cluster implication for $P < .01$. In this study, the covers were made for the sections involved in the DMN. Ultimately, the DMN covers were used in the FC analysis after combining them.

2.6. Functional connectivity analysis

The FC analysis data were calculated within the REST in Matlab (http://www.restfmri.net/forum/). We determined the mean time duration for the DMN and calculated the functional connectivity of the DMN. Later, the average correlation values were transformed into z values via z-transformation, while enhancing the normal distribution.[32] With the values obtained, we created the final FC map exposed to the z-transformation to compare the groups.

2.7. Statistical analysis

To analyze the demographic data, we employed the two-sample *t*-test to compare continuous variables, and the Chi-Squared test for comparing categorical data via the IBM SPSS 22.0. The two-sample *t*-test was used to create the individual-level FC map and to measure the discrepancies in the FC regional group. Then, in the DMN mask, the two-sample *t*-test was applied via voxel-wise cross-subject statistics to analyze the FC maps. For multiple comparisons, the gaussian random field theory was applied to modify the level of significance ($P < .01$).

2.8. Correlation analysis

FCs are reserved for nonstandard values in brain areas. Followed by evaluating the results normalcy, Pearson correlations were calculated within the variables based on $P < .05$ in statistics with the IBM SPSS 22.0.

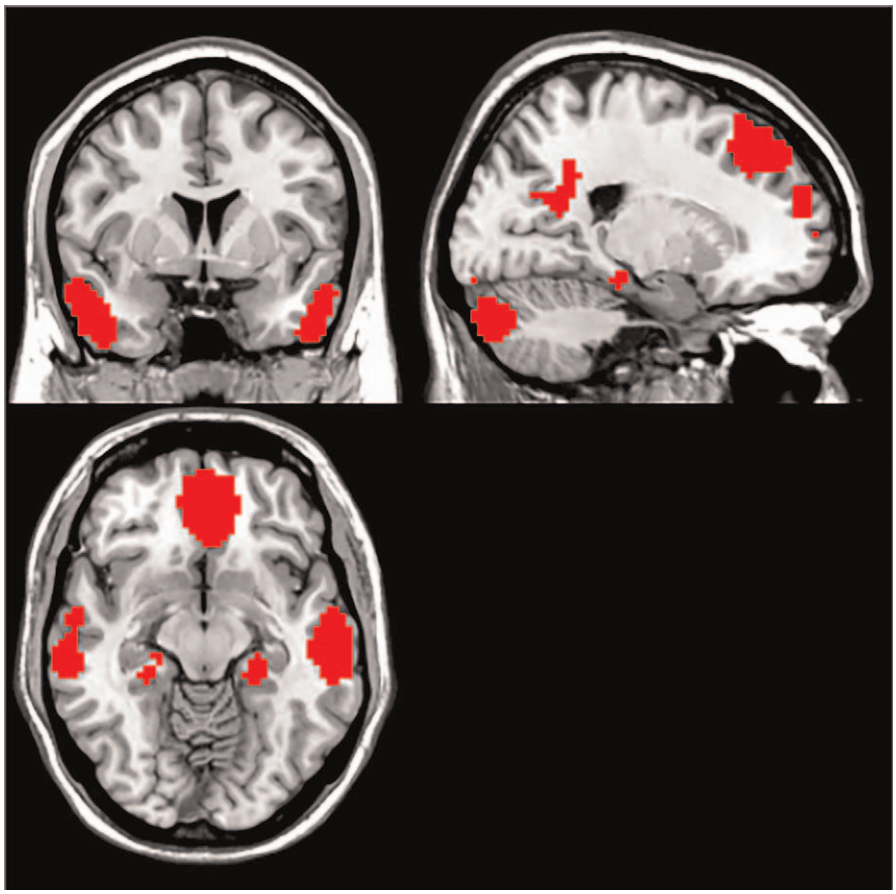

Figure 1. The default mode network (in terms of group ICA with the threshold at z≥5).

3. Results

3.1. Demographics and clinical characteristics of the subjects

Table 1 represents the demographic characteristics of the participants. No statistically significant difference was found within the 2 groups regarding age, gender, and education level ($P = .44$, $P = .86$, $P = .27$).

3.2. DMN Maps as determined by group ICA

ICA was used to eliminate the DMN masks from the control group. The sections included in the DMN contained the bilateral medial prefrontal cortex, PCC/ precuneus, lateral temporal cortex, ventral anterior cingulate corte and cerebellum Crus 1 and Crus 2, and parietal lobes (medial, inferior, and lateral) (Fig. 1).

3.3. Group differences in DMN in terms of FC

We found significant group differences of FC values with the two-sample *t*-test comparing patients and controls in the DMN masks. Compared to the controls, depressive patients presented significantly decreased FC in the left middle orbitofrontal gyrus (MOFG) and right superior marginal gyrus (SMG) (Table 2, Fig. 2)

Table 2

Signification differences in FC values between the groups.

Cluster location	Peak (MNI) X	Y	Z	Number of voxels	*T* value
patients<Controls					
Left MOFG	−3	45	−12	182	−5.19
Right SMG	54	−48	33	62	−4.35

MNI = montreal neurological institute, MOFG = medial orbitofrontal gyrus, SMG = superior marginal gyrus.

3.4. The relation between FC and the clinical variables

Our results showed significant group differences in 2 areas (left MOFG and right SMG). Pearson linear correlation analysis was used to detect correlations among FC and HAM-D scores in the patient group. The results indicated a negative correlation between HAM-D scores and abnormal FC values in the right SMG and no significant correlations were found between FC values with those clinical variables (Fig. 3).

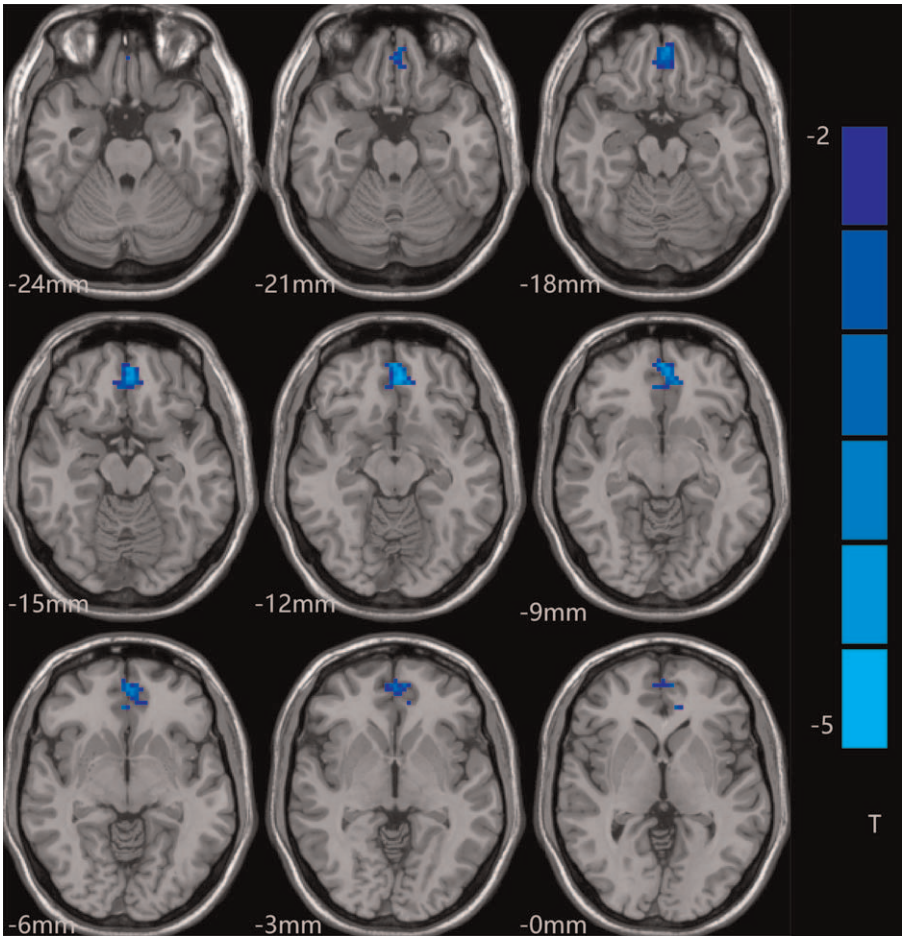

Figure 2. The FC alterations in the left MOFG and right SMG (Blue denotes lower FC. The values of color bars point T found from two-sample *t*-test (FC is the contraction of functional connectivity).

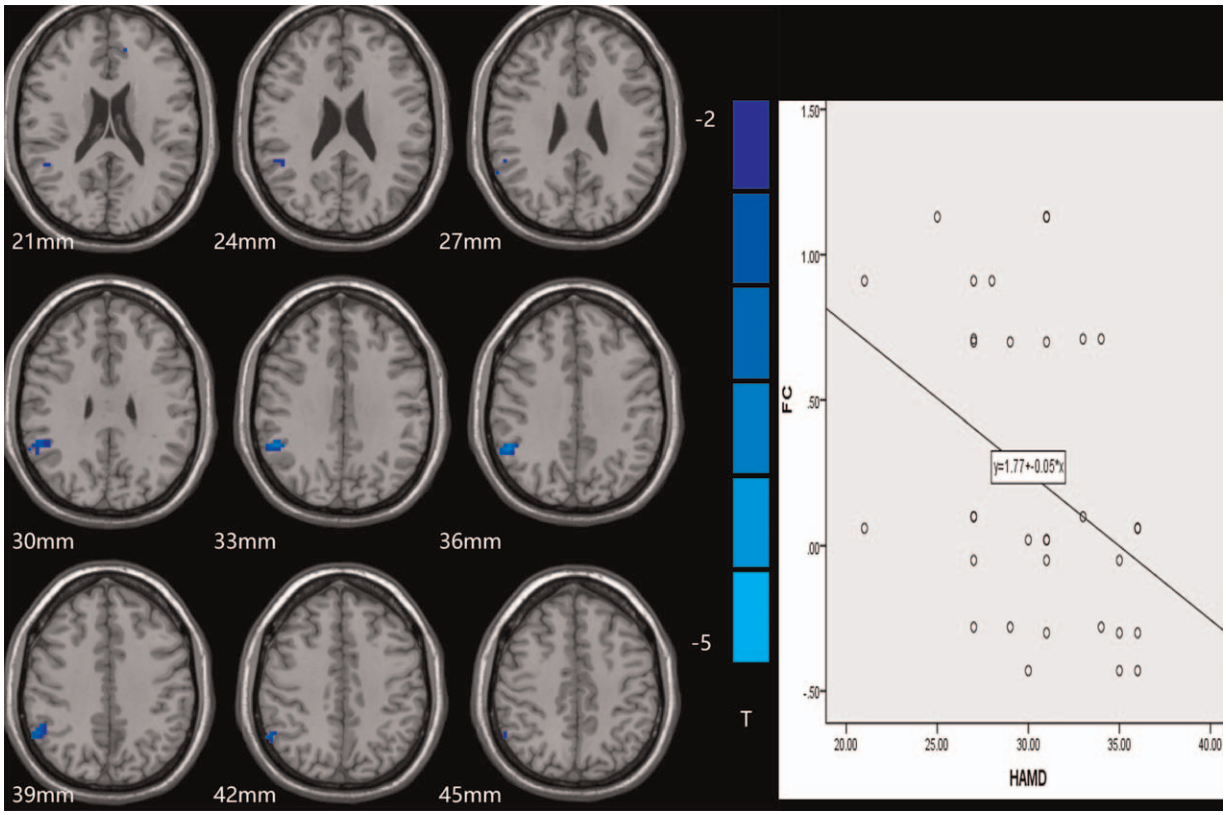

Figure 3. FC differences in the left MOFG and negative correlation between the FC values in the left MOFG and HAM-D scores.

4. Discussion

Compared to the traditional magnetic resonance imaging data analysis methods, the ICA technique, which was developed by solving the blind source separation technology, is a more flexible technique that allows to analyze the functional magnetic resonance imaging data. Hence, it reduces the hypothesis of cerebral hemodynamic response and time constraints, which can be utilized with no preceding time series associated with a priori. We assumed that the total area of the brain can be broken down into some principal components, each of which can be used to define a particular functional area. In our study, we observed that treatment-naive, first-episode MDD patients had reduced FC in the left MOFG and right SMG compared to controls. Furthermore, a negative correlation was found between abnormal FC values in the right SMG and HAM-D scores-meaning that abnormal FC values correlated with more severe symptoms presentation.

The SMG is a key area in the DMN, located in the junction between the temporal lobe and parietal lobe. It is situated in a part of the superior parietal lobule of the brain system, in charge of emotions and memory processing. Interestingly, this area is also related to performing home activities. Structural changes of the SMG were reported in earlier imaging investigations on MDD.[35,36] A meta-analysis of volumetric studies found that volume reduction of the SMG in MDD.[37] Yu et al found fALFF-values of right SMG indicating hypoactivation in unipolar depression patients, but reduced fALFF-values of right superior parietal lobule in bipolar depression patients.[38] Additionally, Han et al found volume reduction of the marginal gyrus and superior parietal lobule in MDD, suggesting that the gene and its epigenetic variations could have influenced the morphologic variations of SMG. They concluded that this procedure may be related to MDD development.[39] Our findings suggest that a significant correlation between reduced FC values in the right SMG is related to severity of symptoms in treatment-naive, first-episode MDD patients, what could represent a known avenue for understanding some pathophysiology of depression.

The MOFG is a considerable and integrative structure exhibiting extensive connectivity with cortical and subcortical areas, which straightly connects thalamus and anterior-posterior cingulate cortex (PCC). Thalamus has been shown to be related to emotional regulation.[40] The PCC is implicated in different key cognitive and behavioral functions, such as self-processing consciousness and executive function.[41,42] In this work, we found a reduced FC of MOFG in treatment-naive, first-episode MDD patients. We speculate that abnormal FC in MOFG could influence PCC and thalamus to indirectly impair the DMN. As we know, the DMN has a crucial role in emotional thoughts and cognitive function. In addition, Burks et al found that OFG is a key midpoint for emotional information through diffusion tensor imaging-based fiber tracking.[43,44]

Reduced OFG volume was found in patients with major depression,[45,46] suggesting a role of the OFC in the pathophysiology of major depression. Moreover, Frodl et al found that imbalance of OFG functional connectivity in depression patients appears to signify a neural mechanism of the treating bias though a task-state functional magnetic resonance.[47] Functional abnormalities in OFG are highly interconnected areas that are well-known from human and animal lesion.[48] Our results showed a negative correlation between abnormal FC values in the

right SMG and HAM-D scores and a reduced FC in MOFG, which could be somewhat related to rumination and emotional processing in depressive patients.

4.1. Limitations

Besides a small sample size, other limitations of our study would be worthy of mentioning. First, the impacts of physiological noise including heart and respiratory rhythm in the resting state cannot be totally removed. Second, this study focused on the DMN, aiming to contribute to a better comprehension of the role neurophysiological abnormalities of the DMN might play in depressive patients. Consequently, we may have excluded some results from other brain areas outside the DMN. Third, the participant patients had an age variation ranging from 18 to 30 years. We could not eliminate possible confounding variables regarding age differences although the illness period was employed as a covariate in the present work.

5. Conclusions

Our study found discrepancies in FC values between depressive patients and controls. Reduced FC in the left OMFG and SMG was found in treatment-naive, first-episode MDD patients compared to healthy subjects. Moreover, a negative correlation was found between abnormal FC values in the right SMG and HAM-D scores, suggesting that OMFG and SMG may be areas of interest for better comprehension of the neurobiology of MDD.

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Conceptualization: Renqiang Yu.
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Visualization: Gang Peng.
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Writing – original draft: Renqiang Yu.
Writing – review & editing: Renqiang Yu, Zhiwei Zhang, Fajin Lyu.

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